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COMBINED SYPHILITIC AND RHEUMATIC DISEASE OF THE AORTIC VALVE

REPORT OF THREE CASES

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Authentic cases of combined syphilitic and rheumatic disease of the aortic valve are extremely rare. In a thorough investigation of the last six thousand, five hundred postmortem examinations performed at the Mount Sinai Hospital during the past twenty years only two acceptable cases could be found. A search of the literature failed to disclose any similar observations except possibly Stolkind's [1] case of syphilitic aortic insufficiency with mitral stenosis; in that case the absence of a microscopic description does not permit us to exclude the possibility of coexistent rheumatic disease in the aortic valve.

Combinations of rheumatic disease of the heart with syphilis of the aorta found at necropsy are, however, less rare. Cabot [2] (1926) stated that "rheumatic valve lesions rarely accompany syphilitic aortitis." Reference to the table indicates the various combinations of these diseases reported in the literature together with seven cases investigated by us. The syphilitic process was entirely supravalvular in four of the cases, while commissural syphilis was present in the remainder; the three latter cases are reported in detail.

Buday [3] and Reid [4] referred statistically to the association of rheumatic with syphilitic disease of the heart. The former enumerated ten cases of combined "syphilitic endocarditis" and "endocarditis chronica fibrosa"" among approximately eight hundred specimens of endocardial

From the laboratories of the Mount Sinai Hospital.

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1. Stolkind, E. J.: Brit. J. Child. Dis. **17**:126, 1920.
2. Cabot, R. C.: Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926, p. 336.
3. Buday, L.: Frankfurt. Ztschr. f. Path. **38**:450, 1929.
4. Reid, W. D.: Am. Heart J. **6**:91, 1930.

disease. The latter stated that of seventy-eight cases of cardiovascular syphilis, two were definitely associated with rheumatic disease of the heart. In the absence of protocols it is impossible to evaluate these cases, particularly with reference to combined rheumatic and syphilitic disease of the aortic valve.

The following cases illustrative of combined rheumatic and syphilitic disease of the aortic valve are reported.

REPORT OF CASES

CASE 1.—A Puerto Rican driver, aged 27, was admitted to the medical service of Dr. Leo Kessel on Feb. 3, 1932. He was discharged from the hospital on Feb. 11, 1932, and returned to the admitting office on the following day, when he died of pulmonary edema.

History.—The patient had varicella in childhood and admitted having had two attacks of gonorrhea at the age of 17. He had married seven years before admis-

Cases of Syphilitic Aortitis Combined with Various Types of Rheumatic Disease of the Heart

Author	Aorta	Aortic Valve	Mitral Valve
Cabot's case of syphilitic aortitis with rheumatic myocarditis (New England J. Med. **201**: 177, 1929)	Syphilitic	Normal	Normal
Dumas and Brunat (Lyon méd. **139**: 577, 1927)	Syphilitic	Normal	Rheumatic
Gallavardin and Gravier (Lyon méd. **145**: 541, 1930, cases 3 and 6)	Syphilitic	Rheumatic	Normal
Gallavardin and Gravier (Lyon méd. **145**: 541, 1930, cases 4 and 5) and four cases in necropsy material of the Mount Sinai Hospital	Syphilitic	Rheumatic	Rheumatic
Stolkind [1]	Syphilitic	Syphilitic	Rheumatic
Cases 1, 2 and 3 of this report	Syphilitic	Syphilitic and rheumatic	Rheumatic

sion, and his wife had died about six years later from a postpartum hemorrhage. There were four healthy children. The family history was irrelevant. Eight years before, shortly after his arrival from Puerto Rico, the patient was in another hospital in New York with an attack of acute polyarthritis. Since then there had been pain and stiffness in the joints in rainy weather. There was no known cardiac involvement. He felt perfectly well until one month before hospitalization, when he noticed dyspnea and palpitation on climbing stairs. Three weeks later a nonproductive cough appeared. For the past three days there had been sharp, nonradiating epigastric pain.

Physical Examination.—The patient appeared well developed, undernourished and chronically ill. His temperature was 99.4 F.; the pulse and respiratory rates were 96 and 20 per minute, respectively. The pupils were normal. The trachea was in the midline and freely movable. The great vessels of the neck pulsated forcibly, and a murmur could be heard over them. The cervical, bilateral axillary, inguinal and epitrochlear nodes were palpable, those in the right axilla being the size of walnuts. The lungs were normal. The heart was enlarged to the left and downward, its point of maximum impulse being located in the sixth left intercostal space 1 inch (2.54 cm.) to the left of the nipple line. A diastolic thrill was felt over the entire precordium. At the apex a blowing systolic murmur trans-

mitted to the axilla was heard; a diastolic murmur of maximum intensity was present in the second left intercostal space at the base. The second aortic sound was louder than the second pulmonic. The rhythm was regular. The radial pulses were equal, regular and markedly Corrigan in type. Pistol-shot sounds were heard over the femoral arteries, and capillary pulsation was noted. The abdomen was diffusely tender, especially in the epigastrium. The neurologic status was negative.

Laboratory Data.—The Wassermann and Kahn reactions of the blood were positive (4 plus). The hemoglobin was 80 per cent (17 mg. per hundred cubic centimeters of blood equals 100 per cent). There were 10,200 leukocytes per cubic millimeter of blood, of which 70 per cent were polymorphonuclear cells, 26 per cent lymphocytes and 4 per cent myelocytes. The sedimentation rate for erythrocytes was normal. The blood pressure was 154 systolic and 20 diastolic as determined on the right arm, and 130 systolic and 20 diastolic as determined on the left. The specific gravity of the urine was 1.032; an occasional trace of albumin and a few constant leukocytes were found. Roentgen examination of the chest showed a hypertrophy with marked dilatation of the left ventricle. An enlargement of the heart to the right was also noted. No abnormality was observed in the lungs.

Course.—The temperature rose to 101 F. soon after admission to the hospital but rapidly dropped to and remained normal as the abdominal pain disappeared. The patient was discharged as asymptomatic on the eighth day, but on the following day he became desperately ill and was brought to the hospital where he immediately died.

Clinical Diagnosis.—The diagnosis was chronic rheumatic cardiovalvular disease, aortic insufficiency, mitral insufficiency (and stenosis), recurrent rheumatic fever and syphilis.

Postmortem Examination.—This included an examination of the brain. The heart (fig. 1) weighed 625 Gm. The pericardium was smooth and glistening, except over the apex anteriorly where there was a fibrous filiform adhesion. It was enlarged markedly to the left, the apex being formed entirely by the left ventricle. The right auricle was normal. The right ventricle was dilated and hypertrophied. The tricuspid valve was normal. The pulmonary cusps were thin except for the anterior one which showed a slight localized thickening of the free edge. Toward the base of this cusp on its ventricular side were two lesions, a pink, round, slightly elevated flat-topped one about 3 mm. in diameter and another smaller, more grayish one just above. About 1 cm. above the anterior cusp in the pulmonary artery there was a flat, pink, round, finely corrugated and slightly raised lesion approximately 4 mm. in diameter. The left auricle was slightly dilated. Rising from the posterior leaflet of the mitral valve was a slightly raised, pinkish-gray corrugated roughening of the posterior wall of the left auricle. The anterior leaflet of the mitral valve was considerably thickened and vascularized. The chordae tendineae at this portion of the valve were white and thickened. The valvular insertions were broadened. There were no verrucae on the valve. The posterior leaflet was also thickened, and branching vessels could be seen on its auricular surface. The left ventricle was enormously dilated, and the chamber was globular, affecting both the inflow and the outflow tracts. The myocardium of the left ventricle was hypertrophied and grayish red. The posterior papillary muscle was markedly hypertrophied except for its apex, which was atrophied and gray. The right half of the anterior papillary muscle was almost entirely atrophied. The musculi pectinati were rather prominent. The ventricular endocardium was gray throughout. The cusps of the aortic valve were irregularly thickened, white,

retracted and rolled inward. The edges of the leaflets and the corpora Arantii were completely inverted. There were a number of irregular thickened endocardial streaks representing early pockets of regurgitation in the subaortic region and upper outflow tract. They were also seen on the ventricular aspect of the anterior leaflet of the mitral valve. There was a slight separation of all the commissures, especially the left posterior commissure. Rising above each commissure in the aorta was a bluish-white circular lesion with scalloped edges, the surface of which was raised and irregularly corrugated. The lesions measured from 1.5 to 2 cm. in diameter. Above and adjacent to them were several small and similar lesions about 2 or 3 mm. in diameter and a larger elevation at the beginning of the transverse arch of the aorta. There was an accessory coronary ostium just anterior to that of the right coronary artery. This corresponded to the first anterior descending branch of the right coronary artery which otherwise ran a normal

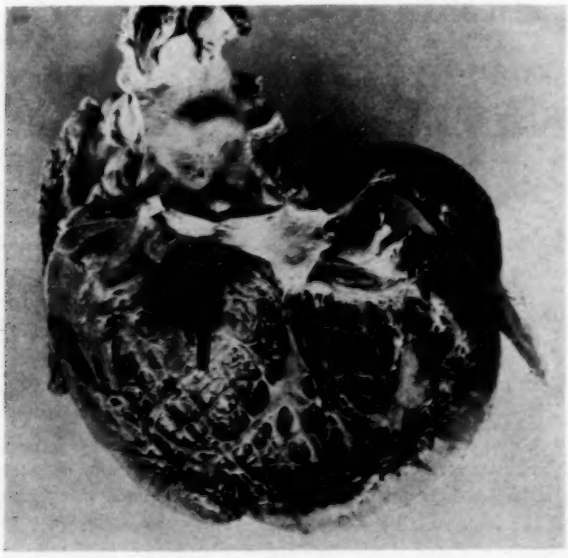

Fig. 1 (case 1).—View of the left ventricular cavity. Supravalvular syphilitic mesaortitis with involvement and separation of the commissures and rolling and thickening of the cusps. Chronic fibrous rheumatic aortic and mitral valvulitis.

course. The left coronary orifice was normal. The orifices were not raised. There was slight atherosclerosis of the coronary arteries without narrowing of the lumen. The thoracic descending aorta showed no changes.

For histologic study in this case and case 2, blocks of cardiovalvular tissue were cut according to the standardized method described by Gross, Antopol and Sacks,[5] and additional blocks of tissue were cut wherever indicated. In the three cases at least two slides were stained from each block, one with hematoxylin and eosin, the other with Weigert's elastic and van Gieson's connective tissue stains.

Microscopic Examination.—Aorta and Left Aortic Valve: The architecture of the aorta (fig. 2*A*) was entirely destroyed. No clear differentiation of the

5. Gross, L.; Antopol, W., and Sacks, B.: Arch. Path. **10**:840, 1930.

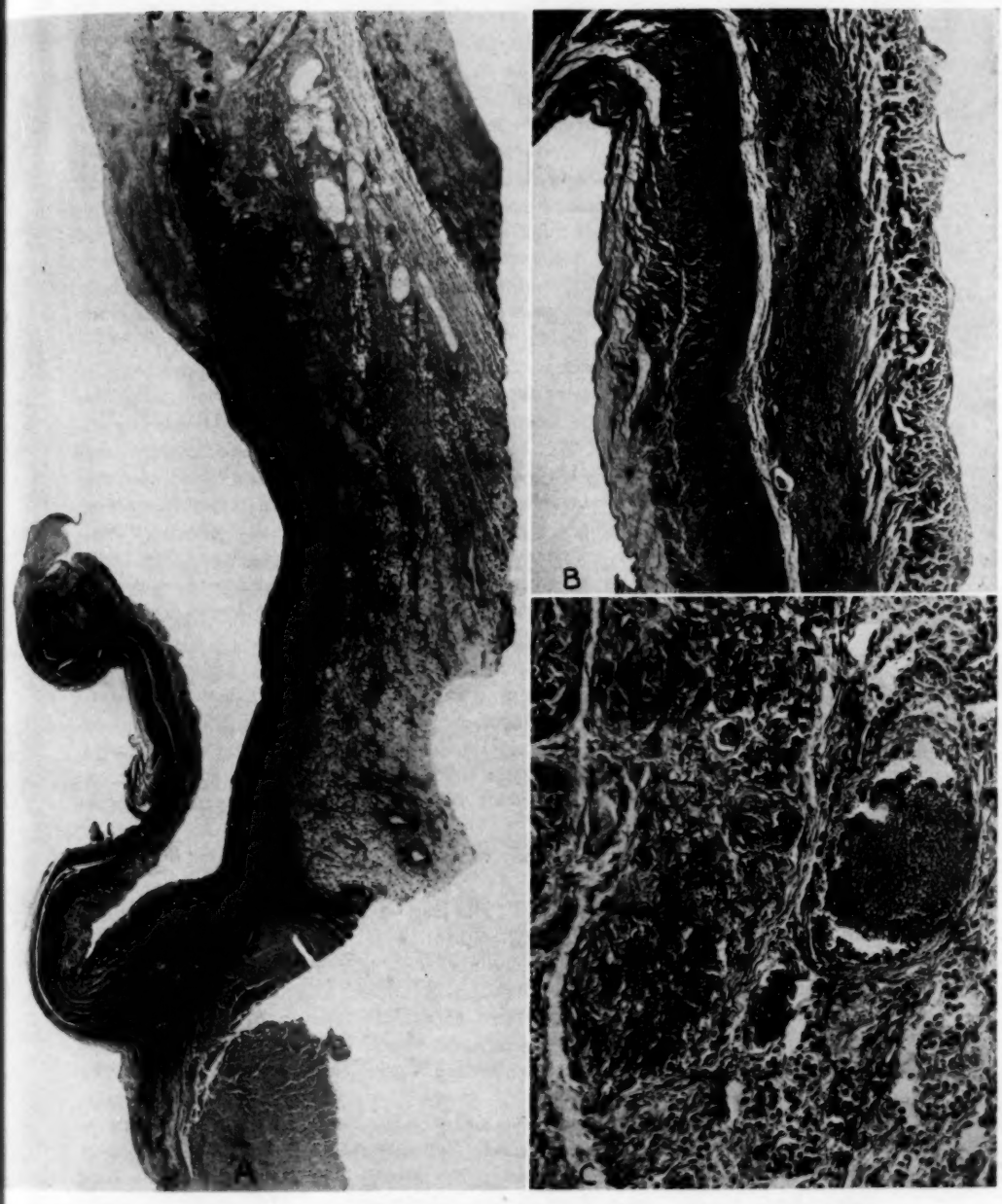

Fig. 2 (case 1).—*A*, aorta and left aortic cusp (midportion). The syphilitic mesaortitis ends above the sinus of Valsalva and involves the adventitia of the pulmonary artery by contiguity. The valve leaflet is markedly thickened and rolled because of chronic fibrous rheumatic valvulitis. Weigert's elastic and van Gieson's connective tissue stain, reduced from × 7. *B*, higher power of the body of the cusp in *A*, showing the vascularized broad fibro-elastic reduplications characteristic of chronic rheumatic valvulitis. Hematoxylin and eosin; reduced from × 50. *C*, commissure between the left and right aortic leaflets showing intense syphilitic inflammation with destruction of elastica, vascularization and marked infiltration with plasma cells. Weigert's elastic and van Gieson's connective tissue stain; reduced from × 200.

normal coats was possible. In certain areas the media was recognizable only by a few wiry twists of elastica embedded in dense richly vascularized fibrous tissue. The intima showed a typical fibro-elastic hyperplasia with little accumulation of fat, sometimes reaching a thickness in excess of that of the media. Blood vessels extended through the media into the outer zone of the intima. The adventitia was thickened and fibrous; the vasa vasorum were narrowed by an elastic hyperplastic intimal process. The vessels and a few of the nerve bundles were surrounded by dense aggregations of plasma cells, lymphocytes, endothelial cells and fibroblasts. The mesaortitis ceased abruptly at the upper margin of the sinus of Valsalva.

The adventitia of the attached pulmonary artery was similarly involved by obvious extension from the adventitia of the aorta.

The ring [6] of the aortic valve was densely fibrous, well vascularized and sparsely infiltrated with lymphocytes. The valve leaflet was thickened, and its free edge was knoblike. The thickening of the valve (fig. 2*B*) was due to a broad musculofibro-elastic thickening on the ventricular side of the ventricularis layer [6] of elastica. The latter was also thickened and contained many bundles of smooth muscle, blood vessels with well developed muscularis and a scattering of lymphocytes. The knoblike free edge was composed of concentric whorls of dense fibrous tissue and thick elastic strands; blood vessels penetrated into the center of the knob.

The Levaditi stain revealed no spirochetes in the section.

Commissure Between the Left and Right Aortic Leaflets (fig. 2*C*): The same type of lesion described in the aorta was seen. The process, however, instead of ceasing abruptly, extended unchanged in character or degree into and behind the annulus fibrosus considerably below the level of the insertion of the valve. Here there was much irregular elastic tissue showing increase and destruction, dense foci of plasma cells and arterioles with marked intimal hyperplastic thickening.

A typical perivascular Aschoff body was seen in the interventricular myocardial crest adjoining the annulus.

Mitral Valve (Posterior Leaflet): The ring [7] of the mitral valve was fibrosed and vascularized. There was a focal infiltration of polymorphonuclear cells and lymphocytes. The valve was markedly thickened by a hyperplastic process composed of a widened auricularis layer of elastic fibers, and on the auricular side of this layer was a wide band of collagen fibers, fibroblasts and bundles of smooth muscle. In the auricularis layer were many blood vessels with well developed muscular coats. A few perivascular Aschoff bodies were seen in the adjoining left ventricular myocardial septums.

Pulmonary Artery (Section Through the Lesion Noted in the Gross Description): In a localized area the media was distinctly thickened. The medial elastic fibers were discontinuous and showed rather abundant connective tissue between them. Blood vessels, some of which were thickened, coursed through the media

6. In the semilunar valves the "ring" represents the proximal end of the valve leaflet constituted by the triangular ring spongiosa and adjacent portion of the fibrous annulus. The terminology of valve structures is that employed by Gross, L., and Kugel, M. A. (Am. J. Path. **7**:445, 1931).

7. In the auriculoventricular valves the "ring" represents the proximal portion of the valve limited above by the apex of the auricular myocardial wedge and consisting of ring spongiosa and the adjacent portion of the annulus fibrosus (Gross and Kugel [6]).

to end in the intima, which was only slightly thickened. There were no cellular infiltrations in the middle coat. Many of the adventitial vessels revealed moderate intimal hyperplasia. There were sparse aggregations of lymphoid cells in the adventitia without particular perivascular distribution.

The peripulmonary epicardium was thickened, and there were small foci of mononuclear and plasma cells directly beneath the mesothelium.

Pulmonary Valve (Section Through the Nodular Lesion on the Anterior Leaflet): The ring was fibrosed and vascularized, and the annulus fibrosus was infiltrated by a few mononuclear and polymorphonuclear cells. Toward the base of the pulmonary valve, external to the ventricularis layer of elastica, there was a large hyperplastic elevation characterized by proliferation of fibrous, muscular and elastic tissue and by numerous large arterioles with extremely thick muscular walls. There was some disintegrating hemoglobin pigment beneath the endothelium. Several macrophages filled with brown iron-containing pigment were also seen here. The remainder of the valve and pulmonary artery in this section was entirely normal. There was a chronic epicarditis around the root of the pulmonary artery, as evidenced by proliferating endothelial cells, collections of plasma cells and lymphocytes, numerous young and old capillaries (many with proliferation of the lining endothelium) and a thickening of the submesothelial fibrous tissue.

Left Ventricle: Typical perivascular Aschoff bodies were found in the myocardial septums. There was a marked hypertrophy of the myocardial nuclei. Several arterioles showed intimal hyperplasia compromising the lumens to a slight extent. The larger coronary arteries were normal. At various points the endocardium was thickened by a vascularized musculofibro-elastic hyperplasia. Elsewhere there were palisade infiltrations of polymorphonuclear leukocytes, mononuclear cells and cells with gnarled and twisted nuclei.

Left Auricle: The left auricle was normal.

Summary.—The aorta showed syphilitic mesaortitis; the aortic valve, old rheumatic valvulitis and syphilitic involvement of the commissures; the mitral valve, typical old rheumatic valvulitis; the pulmonary artery, probably focal healed pulmonary mesarteritis; the pulmonary valve, focal, nodular old rheumatic valvulitis; the myocardium, typical Aschoff bodies in the left ventricle; the endocardium, rheumatic mural endocarditis of the left ventricle; the epicardium, chronic low grade epicarditis around the great vessels and at the base of the heart, probably syphilitic, by contiguity with the adventitia of the aorta.

Case 2.—An unmarried American colored woman, a domestic, aged 36, was admitted to the medical service of Dr. A. A. Epstein on Sept. 2, 1926, and died September 7.

An attack of acute rheumatic fever occurred at the age of 9 years, and influenza at 28. The patient stated that she had not had venereal disease. No significant information was obtained in regard to the family history. The patient was known to have had cardiac disease since the age of 14 years. For the past twenty years she had had dyspnea on exertion, precordial pain, mild edema of the ankles and frequent sore throat. Three months before admission to the hospital all the cardiac symptoms had become aggravated and the patient was forced to go to bed. Drenching night sweats, chills and fever appeared. A slight cough and some orthopnea were noted recently with marked loss of weight and strength. Three days prior to hospitalization she began to have pain in the left hypochondrium, and the edema of the ankles subsided. Sanguineous sputum was expectorated.

Physical Examination.—The patient was undernourished, acutely ill, dyspneic and perspiring; her temperature was 103 F.; the pulse and respiratory rates were 120 and 26 per minute, respectively. The pupils were normal. There were forcible arterial pulsations in the neck. Dulness was present at the base of the right lung; there were a few fine crackles over this area; bronchial breathing and moist râles were heard in scattered areas of the left lung; auscultation revealed a coarse frictional rub in the left axilla. Over the fifth and sixth left intercostal spaces outside the nipple line a presystolic thrill and a sharp apex beat were palpated. Systolic and diastolic murmurs were heard at the apex; a loud diastolic murmur was also present at the base, being transmitted downward close to the left border of the sternum; at the aortic area there was, in addition, a rumbling systolic murmur. The rhythm was regular; the radial pulses were equal and Corrigan in type. The left side of the abdomen was exquisitely tender and held rigidly. The edge of the spleen was, nevertheless, palpable. The liver could not be felt. There was no edema or clubbing of the fingers. The neurologic status was negative except for sluggish ankle and knee jerks.

Laboratory Data.—The Wassermann reaction of the blood was negative. The hemoglobin was 40 per cent. There were 3,000,000 erythrocytes and 12,600 leukocytes per cubic millimeter of blood. Of the latter, 84 per cent were polymorphonuclear cells. A culture of the blood yielded abundant numbers of Streptococcus anhaemolyticus (viridans) in all the mediums. The blood pressure was 125 systolic and 50 diastolic. The specific gravity of the urine was 1.018; there were a trace of albumin and many erythrocytes and leukocytes. A bedside roentgen examination of the chest disclosed no abnormality in the lungs.

Course.—Two days after admission the patient became stuporous, and auricular fibrillation was observed. Death supervened three days later.

Clinical Diagnosis.—A diagnosis of chronic rheumatic cardiovalvular disease, mitral stenosis and insufficiency and aortic insufficiency, subacute bacterial endocarditis, infarction of the spleen and bronchopneumonia was made.

Postmortem Examination.—This included examination of the brain. The heart weighed 530 Gm. and was normal in shape and position. The musculature was normal in consistency. The pericardium was smooth and contained a normal amount of clear straw-colored fluid. The aorta was flexible and presented slight evidence of atherosclerosis. The visceral pericardium contained smooth, pearly-white pericardial thickenings, one situated at the anterior aspect of the right ventricle and almost 2 cm. in thickness. Several other smaller thickenings of the visceral pericardium were situated over the anterior aspect of the left ventricle near the apex and at the posterior aspect of the right ventricle. The endocardium of the right auricle was irregularly grayish white. The foramen ovale was closed. The tricuspid valve measured 8.5 cm. in circumference. At the junction of the anterior and mesial cusps there was an irregular thickening. The flaps were adherent to the wall of the right ventricle at this point. The scarlike thickening was fibrotic and contained a small amount of lime; the fibrosis extended from the junction of the flaps down on the ventricle for almost 0.5 cm. There was a small subendocardial hemorrhage on the superficial aspect of the scar; the lesion resembled an old healed endocarditis, the nature of which could not be grossly determined. The pulmonary valve was smooth, glistening and competent. The left auricle was somewhat dilated and its wall hypertrophied, measuring almost 1 cm. in thickness in places. The endocardium of the left auricle was irregularly and diffusely thickened. The posterior wall showed wrinkling. The mitral valve

measured 8 cm. in circumference. It was the seat of a healing bacterial endocarditis superimposed on an old chronic valvular disease. The flaps of the valve were thickened, fibrotic and scarred, presumably owing to an old healed rheumatic endocarditis; superimposed on this lesion were irregular, firm, grayish-white bacterial vegetations. At the junction of the two flaps along its line of closure was a flat, firm elevated bacterial vegetation. Extending from the free margin of the flaps at this point and continuing down on the adjacent chordae tendineae, was an irregular, fungoid, friable, grayish-white bacterial vegetation which extended down to the papillary muscle. The vegetation appeared to be a recent process. Along the left lateral aspect of the posterior cusp was an organized bacterial vegetation which extended from the free margins of the flap downward and involved the chordae tendineae. There were also many small flat vegetations on the anterior aspect of the posterior flap which measured 1 or 2 mm. in diameter. These vegetations were fairly well organized. The left ventricle was hypertrophied; its wall measured 2 cm. in thickness. The myocardium was dark brown and firm, and on section revealed areas of fibrosis. The aortic valve measured 6 cm. in circumference and was also the seat of a bacterial endocarditis. Situated between the right and posterior cusps and involving the commissure was a large, irregular, ulcerative endocarditic process 2 by 3 cm. in circumference. It involved the adjacent halves of the cusps and the commissure and extended downward, involving the mural endocardium of the posterior part of the outflow tract of the left ventricle for a distance of almost 1 cm. The vegetation had an ulcerative appearance; it was concave and contained irregular deposits of blood platelet thrombi. The process was situated just anterior to the undefended space, involving it only at its upper margin. The anterior cusp was thickened, and extending from the corpus Arantii there was an irregular, fanlike, friable vegetation measuring 1 by 0.7 cm. The cusps themselves were thickened and fibrotic. The left posterior commissure showed slight separation. The ascending aorta contained puckered scar formations with longitudinal wrinkling which had a pearly grayish-white color, grossly presenting the appearance of syphilitic aortitis. There were also raised irregularly corrugated lesions in the supravalvular region descending well into the right posterior commissure. The orifice of the right coronary artery was slightly narrowed. The main branches of the coronary arteries revealed no gross abnormalities.

Microscopic Examination.—Aorta: There were marked obliterative endarterial alterations in the vasa vasorum of the adventitia with relatively sparse infiltrations of mononuclear cells. Extensive destruction of the elastic tissue of the media was the predominant lesion. The media was largely replaced by the formation of dense scar tissue which was vascularized and infiltrated by mononuclear cells. Superimposed on this was a marked fibro-elastic proliferation of the intima containing a few capillaries.

Right Aortic Cusp: The tip of the cusp was disintegrated by a destructive endocarditis. There was a diffuse valvulitis and, in one place on the ventricular side, a marked proliferation of giant cells. The leaflet contained many channels which were probably vascular. The ring was the site of active inflammation with numerous thick-walled blood vessels (well developed media) and mononuclear cells.

Left Aortic Cusp: No bacterial vegetations were present on this cusp. The leaflet was markedly thickened and shortened and had a bulbous tip formed by large whorls of dense avascular and relatively acellular fibro-elastic tissue produc-

ing inversion of the cusp (fig. 3). The ventricularis elastica was intact although somewhat hyperplastic in its proximal half; the distal portion gave rise to the aforementioned whorls. The ring of the valve was polyvascularized and infiltrated with lymphocytes, histiocytes and large mononuclear cells. The attached section of the aorta revealed the characteristic inflammatory and degenerative lesions

Fig. 3 (case 2).—Aorta and left aortic cusp (midportion). The syphilitic mesaortitis ends above the sinus of Valsalva. The valve leaflet is markedly retracted, thickened and everted. Details of the inflammatory ring lesion are not visible at this magnification. Weigert's elastic and van Gieson's connective tissue stain; reduced from × 3.4.

described; the perivascular cellular infiltrations about the vasa vasorum were, however, more prominent here. It may be added that, whereas the lesions in the medial elastic tissue halted abruptly in the region of the superior limit of the

sinus of Valsalva, the cellular infiltrations of the adventitia continued down to the region behind the annulus fibrosus at the root of the valve.

Aortic Valve Commissures: Section through the left posterior commissure (grossly separated and uninvolved by bacterial endocarditis) revealed extension well into the commissural region of the same aortic lesion described in the aorta, with a subjacent well developed fibro-elastic, vascularized intimal hyperplasia, unassociated with evidence of bacterial endocarditis.

Section through the right posterior commissure (grossly involved by the bacterial endocarditis) showed identical involvement by the aortitic lesion. However, associated with this could be seen thrombo-endocarditic bacterial vegetations on the endocardial surface with a few deeper extensions of foci of acute purulent inflammation into the region of the annulus.

Section Including Posterior Aortic and Anterior Mitral Leaflets: The posterior aortic cusp showed a bulbous fibro-elastic enlargement of the tip similar to that described for the left aortic cusp, with identical vascular and cellular ring lesions. In the subaortic angle (Gross and Kugel [6]) was seen a sparsely vascularized and elastic hyperplastic layer continuing down the ventricular aspect of the anterior leaflet of the mitral valve. The root of the aorta was involved by the aforementioned lesions of syphilitic mesaortitis.

The anterior leaflet of the mitral valve was the seat of a bacterial endocarditis. The substance of the cusp and its ring was extensively vascularized and infiltrated with lymphocytes, histiocytes, large mononuclear cells and occasional polymorphonuclear and fibroblastic cells. The valvulitis involved all the layers of the leaflet, but implicated chiefly the auricular aspect external to the hyperplastic auricularis elastic layer.

Tricuspid Valve: This was normal.

Pulmonary Valve: The valve and artery were normal.

Left Auricle: A few areas of perivascular fibrosis were present in the auricular myocardium. The endocardium was rather poor in elastic fibers. The vascularized subendocardium occasionally dipped down between the auricular myocardic bundles to form wedge-shaped areas infiltrated with lymphocytes and large mononuclear cells.

Posterior Papillary Muscle: Marked interfascicular and perivascular scarring was present.

Myocardium: There was an acute diffuse and focal myocarditis with interstitial infiltrations of lymphocytes, large mononuclear cells and occasional polymorphonuclear leukocytes. A slight amount of perivascular fibrosis was noted. No Aschoff bodies were seen.

Summary.—The aorta showed syphilitic mesaortitis; the aortic valve, chronic rheumatic valvulitis, subacute bacterial endocarditis and a syphilitic commissural lesion; the mitral valve, chronic rheumatic valvulitis and subacute bacterial endocarditis; the myocardium, interstitial myocarditis and perivascular fibrosis.

Case 3.—This case has been made available to us through Dr. W. J. Weiss and Dr. W. Antopol of the Bayonne Hospital and Dispensary. The patient, an unmarried Negro, aged 40, entered the hospital moribund and died shortly thereafter. Under the circumstances, only a sketchy history could be obtained. He had had an attack of polyarthritis fifteen years before his death. Three years later he had a purulent urethral discharge and a sore on the penis. At that time the inguinal glands suppurated and were drained. Two years before his death he was given a series of eighteen intragluteal injections, presumably for syphilis. The patient was asymptomatic until five months before admission to the hospital, when he became short of breath. Since that time he had become progressively worse,

with palpitation, orthopnea, swelling of the feet and abdomen and pain in the upper part of the abdomen. There were no precordial pain, cough or expectoration. On physical examination, he was dyspneic and orthopneic. Râles were heard diffusely throughout both lungs. A diffuse pulsation was present over the left lower part of the chest anteriorly. The heart was enlarged to the left: the apex was situated in the sixth left intercostal space at the anterior axillary line; the right border of the heart was percussed one fingerbreadth to the right of the sternum; a systolic and a diastolic murmur were heard over the entire pre-

Fig. 4 (case 3).—View of the left ventricular cavity. Supravalvular syphilitic mesaortitis with involvement and separation of the left posterior commissure (arrow). Chronic fibrous rheumatic aortic and mitral valvulitis; fusion of the two remaining aortic commissures.

cordium. The cardiac rhythm was entirely irregular (auricular fibrillation). The liver was enlarged, and fluid was demonstrated in the abdomen. Operative scars were present in the right inguinal region. The patient's course was progressively downhill, and he died two days after admission, before a Wassermann test was made.

Postmortem Examination.—The heart weighed 600 Gm. and was enormously enlarged (fig. 4). There were some fibrous (rubbing) tags over the

base of the left auricle, the anterior surface of the right ventricle and the anterior surface of the right auricle. The right auricular cavity was considerably dilated; otherwise it was normal. The tricuspid valve showed fusion of the anterior septal commissure. Approximately at the middle of the anterior leaflet was a small vessel which descends 0.5 cm. from the base toward the free edge. The chordae tendineae to the anterior cusp were slightly thickened. The right ventricle showed marked dilatation of the inflow and outflow tracts. The pulmonary cusps were normal. The pulmonary artery at the base of the right-left commissure was slightly thickened. This was less marked at the right anterior commissure. There was a slight rolling of the center of the free edge of the right pulmonary cusp. The pulmonary artery was somewhat dilated and showed an irregular and wide distribution of delicate puckerings and also several small, slightly raised yellowish plaques with irregular borders, the largest of which was 0.5 cm. in diameter. The left auricle was markedly dilated. The endocardium was thickened. No auricular lesion was grossly detectable. The mitral valve showed a marked universal thickening with typical old rheumatic changes. The anterior leaflet was somewhat elongated. The posterior leaflet showed a rough, rather yellowish deposit on its anterior surface. The chordae tendineae were markedly thickened and fused. There was a definite stenosis of the orifice. On palpating the mitral ring the posterior commissure of the anterior leaflet presented a rubbery feel. On making sections through this region, the tissues occupying the auriculoventricular sulcus showed extensive scarring. The apex of the interventricular septum in this region showed a typical circular gumma 2 mm. in diameter. This gumma lay somewhat anteriorly, reaching almost to the endocardial surface under the mitral pocket. The entire posterior mitral pocket, from its right extremity to approximately 4 cm. toward the left, showed a yellowish puckered thickening of its endocardium which was covered with thrombus for a considerable extent. Additional sections through the auricle, mitral pocket and underlying posterior ventricle, starting from the posterior commissural region of the anterior leaflet and extending toward the left for 4 cm., showed a continuation of the extensive scarring process which involved the lower part of the auricular wedge, the auriculoventricular sulcus and a large portion of the anterior surface of the posterior wall of the left ventricle in this region. Another typical gumma was disclosed 1 cm. to the left of the one previously described. The left ventricle was dilated and hypertrophied. The aortic cusps were thickened. The right posterior and left-right commissures showed typical rheumatic fusion, but the left posterior commissure showed a typical syphilitic separation. The aorta, starting at the insertion of the annulus and continuing up through the entire arch showed a typical syphilitic process with a minimum of sclerotic change. The orifices of the coronary arteries were narrowed by the inflammatory process; the left was only slightly stenotic, while the right measured approximately 2 mm. in diameter. The aortitic process descended several millimeters into the wall of the sinuses of Valsalva and was contiguous with all three commissures, causing, as noted, a separation of the left posterior commissure. Otherwise the coronary arteries were normal.

Microscopic Examination.—Aorta: The architecture was markedly distorted by an infiltrating and sclerotic process. The adventitia was tremendously thickened and fibrosed, containing a considerable amount of new elastic tissue. Marked obliterative endarterial proliferation of the vasa vasorum and dense diffuse and focal perivascular and perineural aggregations of lymphocytes and plasma cells were seen. Large irregular dense fibrous scars, chiefly perivascular, were present in the media with thickening, twisting, rupture and distortion of the elastic fibers.

Innumerable capillaries with perivascular infiltrations of lymphocytes and plasma cells were likewise found diffusely in the media. A few focal areas of necrosis with nuclear débris were situated in the outer third of the media. There was a dense, avascular, noninflammatory fibro-elastic proliferation of the intima which was most marked where the medial lesions were most advanced.

Commissure Between the Left and Posterior Aortic Cusps: The aortitic lesion described continued unchanged into the region of the attachment of the two aortic cusps which grossly showed separation. In addition there was a moderate number of giant cells, occasionally resembling the Langhans type, in the annulus fibrosus.

Left Aortic Cusp: The attached segment of aorta showed the same aortic lesion descending into the wall of the sinus of Valsalva, but ending abruptly at the upper portion of the aortic annulus. The ring spongiosa of the aortic cusp contained several bundles of smooth muscle and many capillaries. The capillaries ascended in liberal numbers throughout the length of the valve cusp in the broad fibro-elastic reduplication situated on the ventricular side of the hyperplastic ventricularis elastica. Toward the closure line a moderate infiltration with lymphocytes was present in the reduplicated layer. The entire cusp was more than double its normal thickness because of the superimposed reduplication (especially at the closure line where the normal thickness was quadrupled). The adjacent crest of the left ventricular myocardium showed a moderate amount of interfascicular and perivascular fibrosis but no Aschoff bodies. The mouth of the left coronary artery was moderately narrowed by thick hyperplastic intimal thickening.

Posterior Mitral Valve: The leaflet was tremendously thickened by extensive fibro-elastic proliferations. The ring of the valve was fibrotic, contained many vessels, often with a hyperplastic intima, and a moderate infiltration with plasma cells and lymphocytes. At this point the auricularis elastica became remarkably hyperplastic, widened and deviated toward the ventricular side of the leaflet by the broad hyperplastic fibro-elastic reduplications, themselves the site of marked vascularization and lymphocytic infiltrations continuous with those at the ring.

The attached segment of left auricular endocardium was sclerotically thickened and slightly reduplicated. The auricular myocardium was normal. The attached crest of left ventricular myocardium showed moderate interstitial fibrosis but no Aschoff bodies.

Mitral Valve at Posterior Commissure: Section through the region of the yellow nodule in the valve pocket showed the valve to be thicker than in the previous portion. Identical inflammatory hyperplastic alterations were present in the leaflet. A typical blood platelet thrombus undergoing organization at the base was present in the valve pocket and was thickest where it overlay the superficially situated necrotic nodule. The nodule had a fairly homogeneous, somewhat basophilic appearance, with scattered cytoplasmic and nuclear débris. This mass of necrotic tissue was surrounded by a more or less irregular zone of granulation tissue containing many capillaries and a dense infiltration of lymphocytes, plasma cells, fibroblasts and histiocytes. Delicate fibrous strands emerged from the inner aspect of this zone to invade the central necrotic area. External to the active granulating zone was a dense, jagged, fibrous capsule which sent prolongations along the adjacent subendocardium and between the myocardial fibers. These strands were likewise infiltrated with lymphocytes and, to a lesser extent, with plasma cells. They contained abundant vessels, which in the region of the auriculoventricular junction, showed extreme intimal hyperplasia, often with complete obliteration of the lumen. There were no giant cells.

Extensive interfascicular and perivascular fibrosis was present in the adjacent left ventricular myocardium. No Aschoff bodies were seen.

Left Ventricle: The endocardium was normal, except for a few small, localized, fibrous thickenings. There was a definite excess of perivascular fibrous tissue, as well as slight, more diffuse interstitial fibrosis. No definite Aschoff bodies were found. There was moderate hyperplasia of the intima of the smaller and larger arteries, often localized or nodular. The epicardium was not thickened, but contained numerous foci of plasma cells and lymphocytes.

Pulmonary Artery: A section through the plaque described grossly showed definite pathologic changes in the adventitia and media. The adventitia was densely scarred by fibro-elastic connective tissue containing blood vessels with a moderate degree of endarterial hyperplasia. About these vessels were collections of plasma cells and lymphocytes. Neither the blood vessels nor the infiltrations descended into the media at this point. The media showed edematous changes between the elastic fibers. The intima was slightly thickened.

Pulmonary Artery and Valve: The pulmonary artery was normal. The ring spongiosa contained a few blood vessels and no cells. The tip of the valve was thickened by an increase of spongy connective tissue on the ventricular side of the ventricularis elastica, but the valve as a whole was free from inflammatory changes. The adjacent right ventricular myocardium was normal.

Commissure Between Right and Left Pulmonary Valves: The pulmonary artery above the commissure was normal. The wedge of media at the root of the pulmonary artery which descends into the commissure was invaded by numerous blood vessels. Those in the outer layers of the media were surrounded by plasma cells. The adventitia and media showed scarring with rupture and increase of the elastic fibers. The valvular endocardium and intima in the commissural region were thickened by dense vascularized scar tissue.

Anterior Tricuspid Valve: The tricuspid valve was normal, except at its insertion, where the ring was invaded by a sheaf of arterioles which descended a short distance into the body of the valve. The annulus fibrosus was slightly thickened. The myocardium was normal. The right auricle was negative. No Aschoff bodies were present.

Summary.—The aorta showed syphilitic (gummatous) aortitis; the aortic valve, old rheumatic valvulitis, syphilitic involvement of the left posterior commissure and aortic stenosis and insufficiency; the mitral valve, old rheumatic valvulitis and mitral stenosis and insufficiency; the left ventricle, gumma of the myocardium and interstitial fibrosis; the pulmonary artery, focal arteritis and inflammation of the commissures of the pulmonary valve; the tricuspid valve, old valvulitis; the epicardium, chronic epicarditis.

COMMENT

The frequency of involvement of the aortic valve in syphilitic mesaortitis has been variously estimated at 10, 28 and 36.5 per cent (Eich,[8] Cabot,[2] and Clawson and Bell [10]). Such valvular involvement [11] generally signifies gross and microscopic descent of the inflammatory process

8. Eich, P.: Frankfurt. Ztschr. f. Path. **7**:373, 1911.

9. Footnote 9 deleted by author.

10. Clawson, B. J., and Bell, E. T.: Arch. Path. **4**:922, 1927.

11. A more detailed description is given by Saphir and Scott (Am. J. Path. **3**:527, 1927; footnote 12), Krischner (Virchows Arch. f. path. Anat. **282**:30, 1931) and Benedict (ibid. **281**:780, 1931).

into the aortic commissures with separation and absorption of the commissural extremities of the cusps. A less common mechanism in the involvement of the aortic valve is weakening and dilatation of the root of the aorta. In either case the free borders of the individual leaflets become too short and incapable of competent diastolic closure. As a result of the tension and friction constantly present in such incompetent valve leaflets it is common to find marked sclerosis, thickening and shortening of the entire leaflet with rolling of the free borders. This is principally true of the valvular defects associated with commissural syphilis. Although the lesion in the body of the aortic cusp may be at times grossly indistinguishable from chronic fibrous rheumatic valvulitis, the etiology of the fibrous deformed aortic valve is nearly always clear in uncomplicated cases of commissural syphilis. However, when associated with mitral stenosis, adhesive pericarditis, old left auricular endocardial lesions or any other clinicopathologic indication of rheumatic cardiovalvular disease, macroscopic estimation of the rôle played by the rheumatic virus in the production of the aortic valvular defect is impossible. Recourse must be had to microscopic investigation.

The histopathology of the aortic valve in syphilitic aortic insufficiency has been described by Saphir and Scott [12] who, in a series of one hundred and seven cases of syphilitic aortic insufficiency with commissural involvement (separation), found inflammatory changes restricted to the commissural extremities of the cusps. The free border of the central portion of the leaflet, although frequently markedly thickened and rolled, was fibrotic, avascular and contained few if any infiltrating cells. Krischner was able to confirm this. Benedict, in a similar group of seventeen cases, presented in detail the microscopy of syphilitic aortic valves, classifying them into "ascending" (in the Monckeberg sense) and "descending" syphilitic types. The latter obviously represents extension to the valve cusp through the commissure, and here Benedict's observations are in agreement with the accepted teachings. With regard to the controversial "ascending" type of extension of the syphilitic process from the sinus wall onto the aortic layer of the leaflet (Benda [13] and Ribbert [14]), he substantiates the observations of thickening and sclerosis in the free border of the cusp, but notes, in addition, extensive formation of new capillaries, congestion and perivascular lymphocytes in the triangular expanse of the spongy connective tissue layer at the base of the

12. Saphir, O., and Scott, R. W.: Am. Heart J. **6**:56, 1930.

13. Benda: Die Gefässe, in Aschoff, L.: Pathologische Anatomie; ein Lehrbuch für Studierende und Aerzte, Jena, Gustav Fischer, 1911; quoted by Benedict.[11]

14. Ribbert: Die Erkrankung des Endocards, in Hencke, F., and Lubarsch, O.: Handbuch der speciellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, quoted by Benedict.[11]

leaflet.[15] He regards the entire anatomic picture as indicative of syphilis. We shall refer to this later.

In order to establish definite histologic criteria for the recognition of syphilitic valvular lesions, we have investigated ten cases of syphilitic aortic insufficiency with commissural involvement in which the history and anatomic findings definitely excluded rheumatism. Microscopic examination of these thickened, deformed aortic valves (studied both near the commissure and in the midportion of the cusp) confirmed many of the observations of Saphir and Scott. At the maximum distance from the commissure inflammatory changes were entirely absent in the cusps in six cases. In three a moderate number of capillaries and round cells were found only in the ring and not in the cusp. In a single instance a more marked ring lesion consisting of thick-walled vessels with endothelial proliferation was found. This was observed to descend by contiguity from the intense syphilitic aortitis immediately above it and to ascend for a short distance into the ventricular side of the base of the leaflet. In short, only one of the ten cases showed inflammatory changes in the cusp per se. (An additional eleventh case showing well developed vascularization of the ring and the ventricular side of the entire length of the aortic leaflet was omitted because rheumatic disease could not be definitely excluded. Capillaries were present in the ring, base and closure line of the anterior cusp of the mitral valve and in the ring of the pulmonary valve. In this case the aortic valvulitis could not be traced as a direct extension from the syphilitic process in the aorta.) Marked avascular and relatively acellular fan-shaped whorls of fibro-elastic proliferation were generally present at the free border of the valve with regular noninflammatory thickening of the fibrous and elastic layers of the root of the cusp. The thickening of the root of the body of the cusp was always less than that at the free border. On the other hand, sections taken near the commissures revealed typical syphilitic chronic inflammatory alterations, most intense at the ring and tapering off as the free border was approached. Immediately adjacent to the commissures the small segment showed diffuse and most intense lesions.

In four additional cases of syphilitic aortic insufficiency showing marked fibrocalcific deforming disease of the aortic valve[16] capillaries and round cells were present in the cusps and rings in three instances. They bore no relation to the distance from the commissure and were apparently reactive changes to lipoid and calcareous degeneration. They are not to be interpreted as of specific inflammatory origin.

15. This has been aptly termed ring spongiosa (Gross and Kugel[6]).

16. These cases will be described in more detail with a group of cases of fibrocalcific disease of the aortic valve to be published.

Although Benedict did not indicate how far from the commissure his sections in the "ascending" type were taken, it is extremely suggestive from our observations that the severe inflammatory lesions he noted in the valve rings were in close proximity to the commissures, which is not representative of the true anatomic condition of the larger midportion of the cusp. In the latter location we were able to find marked inflammatory involvement of the valve in only one of our ten cases. We therefore believe that one must expect, as a rule, to find little or no inflammatory change in this midregion. When any exists, it represents either the rare "ascending" type of extension from the root of the aorta or a horizontal diffusion from the commissures.

In contradistinction to the histologic syphilitic lesions just described are those found in this laboratory by Gross [17] and his co-workers in a large series of cases of chronic rheumatic cardiovalvular disease. Marked vascularization (often arterioles with well developed muscular coats) was found with remarkable constancy in the valve rings, regardless of the distance from the commissures, and in all but inactive cases lymphocytic infiltrations were also present. The aortic cusps themselves were markedly thickened by extensive irregular reduplications of fibrous tissue with varying amounts of vascularization and proliferation of elastic fibers. These layers, the site of inflammatory changes identical with those in the ring, were situated on the ventricular side of the cusp causing deviation (toward the arterial side) of the hyperplastic ventricularis layer of elastica, itself similarly inflamed.

Because of the limitation of syphilitic inflammation to the commissural extremity of the cusp [18] in a great majority of cases, the histologic demonstration of the previously described inflammatory lesions in the midportion of the cusp is indicative of rheumatic valvulitis, even though commissural syphilis is present. In a valve presenting both types of lesions a dual etiology must be considered—commissural syphilis and valvular rheumatism.

Reference to the protocols and figures of our three cases leaves no doubt that they fall into this group of combined syphilitic and rheumatic disease of the aortic valve, the former condition apparent at the commissure, and the latter involving the entire leaflet.

Since isolated syphilitic or rheumatic disease of the aortic valve may present identical clinical pictures, it is impossible to predict definitely the clinical concomitance of the two. When there is anamnestic and clinical evidence of both syphilitic and rheumatic infection, the existence

17. Gross, L.: Personal communication to the authors.

18. This does not take into consideration the extremely rare cases of granulomatous or gummatous involvement of the valves of the heart, examples of which are to be published shortly.

of the physical signs of mitral stenosis or insufficiency leads one to avoid, sometimes unjustifiably, the diagnosis of syphilis of the commissures of the aortic valve. Likewise, if signs of aortic stenosis as well as of insufficiency are present in a syphilitic patient, the diagnosis would almost certainly be uncomplicated rheumatic disease of the aortic valve. (Rarely, fibrocalcific disease of syphilitic aortic leaflets may produce the clinical signs of stenosis; one might incline toward this diagnosis in the presence of a definitely syphilitic lesion at the root of the aorta, i. e., aneurysm, with clinical signs of aortic stenosis and insufficiency and without evidence of organic mitral valve or pericardial disease.)

In case 1 the clinical and laboratory data pointed to the presence of combined syphilitic and rheumatic infection. Because of the relative youth (27 years) of the patient and the predominance of the rheumatic history, the diagnosis of syphilitic valvular disease was not seriously considered clinically. For the same reasons the aortic lesion was submitted to a careful pathologic examination to exclude the possibility of its being rheumatic aortitis. However, the probability that the patient acquired syphilis ten years before death (at the age of 17, when he already had had gonorrhea), the 4 plus Wassermann reaction, the typical supravalvular location of the aortitis and the histologic details leave little room for doubt. A comparison of this case with one of known rheumatic aortitis, which was grossly similar, revealed no striking histologic resemblance, nor did the lesion present any of the characteristics described by Pappenheimer and Von Glahn [19] in rheumatic aortitis.

Case 2 offered no ground for the clinical diagnosis of syphilis. The history and results of physical examination were characteristic of rheumatic disease of the heart and the Wassermann reaction of the blood was negative. The pathologic demonstration of supravalvular syphilitic aortitis descending grossly and histologically into two of the aortic commissures was an unexpected observation.

As in case 1, the clinical findings in case 3 indicated the presence of both rheumatic and syphilitic infection. The extent to which either participated in the evolution of the cardiac syndrome was not clear clinically.

Three unusual pathologic complications in these cases warrant further mention, i. e., the lesion of the main pulmonary artery in the first and third cases, the gumma in the third case and the superimposed subacute bacterial endocarditis in the second.

The etiology of the lesions found in the pulmonary arteries in cases 1 and 3 remains unclear. In these patients the adventitial lesion, with its perivascular collections of round cells and marked intimal hyperplasia

19. Pappenheimer, A. M., and Von Glahn, W. C.: J. M. Research **44**:489, 1924.

of the vasa vasorum, is best explained as an extension by contiguity from the severely inflamed adventitia of the aorta. However, the etiology of the scarred, acellular medial lesions seen in each of these two patients must remain undetermined, since such scars could conceivably be due to either a healed syphilitic or a healed rheumatic lesion. The same attitude must be assumed toward the commissural lesions found in the pulmonary valve in case 3, although in this patient again the location and the type of cellular infiltrations favor the diagnosis of syphilis.

Gumma of the myocardium is a rare lesion, and its presence in case 3 was an entirely fortuitous finding, unassociated with clinical manifestations. This case is also being reported elsewhere.[20]

It is not necessary to comment on the occurrence of subacute bacterial endocarditis in case 2, except to note that it is not a rare complication of either rheumatic cardiovalvular disease or syphilitic aortic insufficiency.

SUMMARY

Three cases of combined syphilitic and rheumatic disease of the aortic valve are reported. In the presence of commissural syphilis, sclerotic deformities of the aortic valve usually occur. When rheumatic lesions are found elsewhere in the heart, it is at times impossible to decide from macroscopic examination alone whether rheumatic disease participated in the production of the aortic valvular defect. By the aid of established histologic criteria for the recognition of rheumatic and syphilitic disease of the aortic valve it is possible to demonstrate such participation, if it exists. Emphasis is placed on the *limitation* of syphilitic changes in the aortic leaflets to their commissural extremities in the great majority of cases, and on the *diffuse* nature of the characteristic lesions of rheumatic valvulitis. Interstitial valvulitis in the midportion of an aortic cusp, particularly with fibro-elastic vascularized reduplications on the ventricular aspect, usually signifies disease other than syphilis (nearly always a rheumatic infection[21]). Association of these two types of histopathologic lesions establishes the existence of combined syphilitic and rheumatic disease in the aortic valve. The rarity of this association is indicated by the fact that it has, to our knowledge, never been previously reported.

20. In a report on rare syphilitic lesions of the heart to be published shortly.

21. In the absence of definite rheumatic manifestations elsewhere in the heart, the etiology of this type of microscopic lesion is still probably rheumatic, although in less characteristic instances it may represent healed lesions of other endocarditides.

HODGKIN'S DISEASE

SEARCH FOR AN INFECTIVE AGENT AND ATTEMPTS AT EXPERIMENTAL REPRODUCTION

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Since the report by Sternberg [1] in 1898 claiming an etiologic relationship between tuberculosis and Hodgkin's disease a voluminous and conflicting mass of evidence has accumulated. This evidence has been discussed in recent reviews by Wallhauser,[2] Simonds,[3] Vasiliu [4] and Chevallier and Bernard.[5]

Interest in the possible tuberculous origin of Hodgkin's disease was rearoused by the reports of L'Esperance,[6] who stated that she was able to produce tuberculosis in chickens and in previously vaccinated guinea-pigs by injection of material from persons with Hodgkin's disease. When the studies to be reported in this publication were begun there were no contradictory or confirmatory reports available. Since then Utz and Keatinge [7] stated that they have confirmatory evidence, which they, however, fail to give. They have already begun the treatment of Hodgkin's disease with chicken serum prepared by injection of material from tissues showing Hodgkin's disease, and they have reported encouraging results in thirty patients so treated.[8]

Branch [9] stated that certain investigators failed to confirm the experimental results of L'Esperance. Of these, Van Es investigated three cases and Aronson two cases. Schulz, on the other hand, isolated acid-fast organisms, apparently of avian type, from a node in one case. More recently van Rooyen [10] reported that he obtained negative results in six cases studied by cultural methods and by inoculation and grafting

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1. Sternberg, C.: Ztschr. f. Heilk. **19**:21, 1898.
2. Wallhauser, A.: Arch. Path. **16**:522 and 672, 1933.
3. Simonds, J. P.: Arch. Path. **1**:394, 1926.
4. Vasiliu, T.: Ann. d'anat. path. **8**:815, 1931.
5. Chevallier, P., and Bernard, J.: La maladie de Hodgkin, Paris, Masson & Cie, 1932.
6. L'Esperance, E.: (*a*) J. Immunol. **16**:37, 1929; (*b*) **18**:127 and 133, 1930; (*c*) Ann. Surg. **93**:162, 1931.
7. Utz, L., and Keatinge, L.: M. J. Australia **1**:397, 1931.
8. Utz, L., and Keatinge, L.: M. J. Australia **1**:521, 1932.
9. Branch, A.: Arch. Path. **12**:253, 1931.
10. van Rooyen, C. E.: Brit. M. J. **1**:50, 1933.

into fowls. Garrod [11] in one case was unable to produce tuberculosis in pigeons. Wallhauser [2] and H. L. Stewart [12] were unable to find evidence of tuberculosis in chickens into which the diseased tissues had been injected.

F. W. Stewart and Doan [13] recently presented immunologic evidence suggesting a relationship to avian tuberculosis. They found that the precipitin titer with tuberculophosphatide in known cases of Hodgkin's disease was within the range observed in known cases of tuberculosis, and that the titer with avian tuberculophosphatide tended to be higher than that with human tuberculophosphatide. These results were not obtained with other types of lymphadenopathies.

The present experiments were designed (1) to test the diseased tissues in a series of fifteen cases of Hodgkin's disease (as well as in eight control cases of different lymphomas) for ability to produce tuberculosis in chickens, guinea-pigs, rabbits, dogs and mice, and (2) to test these same tissues by special cultural methods for the presence of tubercle bacilli. In each case of Hodgkin's disease the diagnosis had been established by examination of microscopic sections of the diseased tissues by two or more experienced, disinterested pathologists, who used as their criterion the classic description by Reed.[14] Lack of space precludes a description of each case in detail. Most of the patients were followed clinically. In the evolution of their disease and in their symptoms, physical signs, response to roentgen therapy and other clinical manifestations they presented typical Hodgkin's disease. Because of the scope of the investigation, the significant but negative results obtained and the objections raised by certain critics to the procedures used by other investigators, the experimental procedures will be given in detail.

EVIDENCE FROM INOCULATIONS AND TRANSPLANTATIONS OF THE DISEASED TISSUES INTO ANIMALS

Experiments were planned to determine the transmissibility of possible infectious agents, whether bacteria or virus, and the transplantability of tissues which may possibly be regarded as neoplastic.

Material from 15 persons with proved Hodgkin's disease was inoculated into 35 chickens, 24 guinea-pigs, 18 rabbits, 7 dogs and 3 mice. Tissues secured at autopsy from suspicious lesions in these animals were in turn used in further attempts at transmission or passage of the disease in 4 chickens, 4 guinea-pigs and 4 rabbits.

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11. Garrod, L. P., in Rose Research on Lymphadenoma, Bristol, John Wright & Sons, Ltd., 1932, p. 105.
12. Stewart, H. L.: J. Lab. & Clin. Med. **18**:281, 1932.
13. Stewart, F. W., and Doan, C. A.: Ann. Surg. **93**:141, 1931.
14. Reed. D. M.: Johns Hopkins Hosp. Rep. **10**:133, 1902.

Similarly conducted control experiments were made in 8 cases of different types of lymphadenopathy. These included 3 cases of lymphosarcoma (1 of reticulum cell type and 2 of lymphocytic cell type), 3 cases of leukemia (1 each of aleukemic myelosis, aleukemic lymphadenosis and chronic lymphatic leukemia) and 2 cases of tuberculous lymphadenitis. These cases were chosen because they were indistinguishable from cases of Hodgkin's disease by their clinical features or by their blood pictures. The biopsy or the subsequent course determined the diagnosis. Inoculations were made into 22 chickens, 15 guinea-pigs, 14 rabbits, 1 dog and 9 mice. Tissues from some of these animals in turn were used in attempted passage of the disease in 7 chickens, 6 guinea-pigs and 6 rabbits. Thus material in 23 cases was injected into 199 animals of different species.

A second type of control consisted of 23 chickens that were not subjected to injections. This group was chosen to provide a check on the occurrence of spontaneous tuberculosis—reputedly common in this species—and on environmental factors. Representative specimens were selected from successive lots of chickens purchased. They were kept in cages alternating with those of the fowl given injections and were subjected to the same environmental conditions.

Experimental Procedure.—The lymphogranulomatous and control tissues were secured aseptically by biopsy or at autopsy. A representative portion of each lymph node or spleen used for injection was prepared for histologic examination. The remainder was chopped and ground in a sterile mortar with sterile physiologic solution of sodium chloride. When the tissue was fibrous the maceration was aided by the use of sterile sand. The suspension was injected as soon as possible, in some instances within two hours after the removal of the tissue. Intravenous injections were made through a 23 gage hypodermic needle. Subcutaneous, intraperitoneal and intracerebral injections were made through a needle of 20 gage or larger. An attempt was made to inject particles that would barely pass through the needles. On the whole rather large doses were used (tables 1 and 2).

Partly grown chickens of both sexes were used. At first they were purchased in the open market. After a tuberculous chicken had been found, all were subsequently purchased directly from a farm. The chickens had been raised in brooders on an open range and were shipped to the laboratory in crates previously unused. In addition, they were tuberculin-tested and kept away from known sources of accidental infection. The conditions of food and environment were not ideal. Certain chickens showed signs of mineral and vitamin deficiency and should have been readily susceptible to infection. After receiving injections they were kept in cages 3 tiers high. Thus there was opportunity for infection of those in the bottom rows with material dropped from those above. The quarters were rather dark, no direct sunlight being admitted. There was little opportunity for exercise. Every chicken received an injection in the wing vein from the suspension described. It was found that despite an occasional immediate death from embolism chickens tolerate coarse suspensions better than do rabbits. In addition to the intravenous injections some chickens were given subcutaneous and intraperitoneal injections.

TABLE 1.—*Experiments in Which Human Tissues Affected with Hodgkin's Disease Were Injected into Animals*

Case	Sex of Patient	Age	Source of Material	Kind of Material	Amount, Gm.	Injections					Animals That Became Tuberculous	Reinjections				Animals That Became Tuberculous
						Guinea-Pigs	Rabbits	Chickens	Dogs	Mice		Diseased Chicken	Guinea-Pigs	Rabbits	Chickens	
1	M	13	Biopsy	Axillary	2.4	2	1	2	..	..	None	....	..	..	..	
2	M	52	Autopsy	Retroperitoneal	10.0	2	2	2	..	..	None	C 4	2	2	2	None
4	M	8	Autopsy	Retroperitoneal	10.0	3	3	3	..	..	Chicken 18	C18	2	2	2	All except 1 rabbit
5	M	27	Biopsy	Cervical, axillary	2.0	3	2	3	..	..	None	....	..	..	..	
7	M	30	Biopsy	Cervical	1.0	..	..	3	..	..	None	....	..	..	..	
8	F	24	Biopsy	Cervical	0.5	..	..	2	..	..	None	....	..	..	..	
10	M	14	Biopsy	Cervical	....	2	2	3	..	..	None	....	..	..	..	
12	M	10	Autopsy	Splenic, tracheal, retroperitoneal	10.0	2	2	3	1	..	None	....	..	..	..	
13	M	28	Biopsy	Cervical	2.0	2	2	3	1	..	None	....	..	..	..	
14	M	30	Biopsy	Cervical	0.5	..	..	3	1	3	None	....	..	..	..	
15	F	19	Biopsy	Axillary	1.0	..	2	2	1	..	None	....	..	..	..	
17	M	21	Biopsy	Cervical	0.5	2	..	2	..	..	Guinea-pig 47	....	..	..	..	
21	F	34	Biopsy	Axillary	3.5	2	2	2	..	..	None	....	..	..	..	
22	M	37	Biopsy	Cervical	0.6	2	..	..	2	..	None	....	..	..	..	
23	F	24	Biopsy	Cervical	1.0	2	..	2	1	..	None	....	..	..	..	
Total (15 cases).....						24	18	35	7	3			4	4	4	

TABLE 2.—*Control Experiments*

Case	Sex of Patient	Age	Source of Material	Kind of Material	Amount, Gm.	Injections: Guinea-Pigs	Rabbits	Chickens	Dogs	Mice	Animals That Became Tuberculous	Reinjections: Diseased Chicken	Guinea-Pigs	Rabbits	Chickens	Animals That Became Tuberculous
Tuberculous adenitis																
11	M	20	Biopsy	Cervical	4.0	2	2	3	..	2	2 guinea-pigs, 2 mice	C56	2	2	2	None
16	F	66	Biopsy	Cervical	0.5	..	..	2	..	..	None	....	..	..	..	
Lymphosarcoma																
3	M	50	Autopsy	Retroperitoneal	10.0	3	2	3	..	..	1 guinea-pig	C13	2	2	2	None
												C15	2	2	2	None
9	M	40	Autopsy	Spleen, retroperitoneal	....	2	2	3	1	3	None	....	..	..	..	
19	F	79	Autopsy	Retroperitoneal	11.0	2	2	3	..	4	None	....	..	..	..	
Leukemia																
6	M	27	Autopsy	Splenic, periaotic	....	2	2	3	..	..	None	....	..	..	..	
18	F	51	Biopsy	Cervical	1.0	2	2	2	..	..	None	....	..	..	..	
20	M	72	Autopsy	Retroperitoneal	....	2	2	3	..	..	None	....	..	..	..	
Controls (no injections given)						..	..	23	..	..	None	....	..	..	..	
Total (8 cases)						15	14	45	1	9			6	6	6	

The rabbits and guinea-pigs received the usual laboratory care. They were kept in hygienic surroundings away from tuberculous animals. Young animals were used and they gained weight rapidly. They were also tuberculin-tested before use. The rabbits were given intraperitoneal injections. In addition, some were given subcutaneous injections. The guinea-pigs usually received subcutaneous injections, but some also received intraperitoneal injections. Transplantation of thin wafers of tissue was made subcutaneously and intraperitoneally into some guinea-pigs and rabbits.

Each dog received an intracerebral injection through a small perforation of the skull in the frontal region. Since tuberculous dogs do not give a cutaneous reaction [15] to tuberculin this test was often omitted. The intracerebral injections were made because of the success reported by Feldman [16] in infecting dogs with avian tubercle bacilli by this method.

After the injections had been given, all animals were watched carefully for signs of disease. They were weighed frequently. Tuberculin tests were performed frequently on the chickens, both avian and human tuberculins of proved potency being used. Old tuberculin 50 per cent of full strength was used in 0.1 cc. doses. At the termination of the experiment some chickens had received seven different tests with each tuberculin. There was no evidence that any of them had been sensitized by the tuberculin of previous tests. The rabbits and guinea-pigs were tuberculin-tested less frequently, but all were tested before the end of the experiment. For these tests, decreasing dilutions of human and avian tuberculins down to that of 1:10 were used.

The animals that did not spontaneously succumb to disease were killed by overanesthetization between the ninth and thirteenth months. The dogs were an exception in that these experiments were terminated between one hundred and two hundred and seventy-four days. All animals were carefully examined grossly at autopsy for evidence of disease. Tissues were then preserved in fixing solution and sections were examined as a routine from lungs, liver, spleen and kidneys as well as from other organs as indicated. All tissues that were tuberculous or that contained lesions even remotely suggesting a granuloma were stained for acid-fast organisms. For this purpose, the Cooper [17] modification of the Ziehl-Neelsen stain was most satisfactory.

Certain animals at autopsy presented lesions the nature of which was uncertain. The tissues showing these lesions were subjected to further study by three methods: 1. Direct smears were stained by the Ziehl-Neelsen method. 2. Cultures were made according to the method described for growing the tubercle bacillus. 3. Passage experiments were carried out (tables 1 and 2) in which these tissues were used for injection into other animals, the methods being used which were employed with the original material.

Results.—The results of the experiments with tissues from persons with Hodgkin's disease are given in table 1; those of the experiments with the control materials, in table 2, and a summary, in table 3. Several experiments deserve special comment.

Of the 35 chickens that received injections of suspensions of tissues from persons with Hodgkin's disease and 22 that received injections

15. Steiner, P. E.: Am. Rev. Tuberc., to be published.
16. Feldman, W. H.: Am. J. Path. **7**:147, 1931.
17. Cooper, F. B.: Arch. Path. **2**:382, 1926.

of suspensions of control tissues, only 1 died of undisputable tuberculosis. In this experiment 3 guinea-pigs, 3 rabbits and 3 chickens received injections of the same retroperitoneal lymph node suspension. Of the 9 inoculated animals, only 1 chicken acquired tuberculous lesions. The patient, a boy 8 years of age, died two years after the onset of symptoms referable to Hodgkin's disease (case 4). One month after injection of the material the tuberculin reaction in this chicken (C 18) was strongly positive. The fowl lost over half of its original weight and died, nine weeks after inoculation, with a massive tuberculous infection of the liver, spleen and lungs. On histologic examination the acid-fast bacilli were present in great numbers. Unfortunately, spontaneous

TABLE 3.—*Summary: Transplantations and Injections into Animals; 222 Experiments*

Diagnosis of Condition of Patients from Whom Tissues Were Taken for Injection into Animals	No. of Cases	Guinea-Pigs		Rabbits		Chickens		Dogs		Mice	
		Injections	Tuberculous	Injections	Tuberculous	Injections	Tuberculous	Injections	Tuberculous	Injections	Tuberculous
Hodgkin's disease	15	24	1	18	0	35	1†	7	0	3	0
Reinjections (passage)	(2)	4	..	4	..	4					
Injected controls:											
Lymphosarcoma	3	7	1	6	0	9	0	1	0	7	0
Reinjections (passage)	(3)	4	..	4	..	5					
Leukemia	3	6	0	6	0	8	0				
Tuberculous adenitis	2	2	2	2	0	5	0	..	..	2	2
Reinjections (passage)	(1)	2	..	2	..	2					
Controls not given injections	..	..	..	..	..	23*					
Total	23	49	4	42	0	91	1	8	0	12	2

* These controls were not given injections but were kept in cages alternating with those of the chickens given injections and were subjected to the same environmental conditions.
† One of the chickens given injections.

tuberculosis cannot be ruled out. This chicken was one of the first in the series and was not tuberculin-tested prior to the injection of the suspension of tissue from the patient with Hodgkin's disease. A suspension of the liver and spleen of this chicken was injected into 2 chickens, 2 rabbits and 2 guinea-pigs. One chicken died with tuberculosis, principally of the liver, in six weeks, and the other, of tuberculosis of the liver, spleen, lungs and bone marrow in nine weeks. One of the guinea-pigs died in six weeks with marked generalized tuberculosis. The second guinea-pig acquired a positive reaction to avian tuberculin but failed to react to human tuberculin; when killed ten months after injection it had only a few scars in the lungs, which on histologic examination could not be definitely identified as tuberculous. Of the 2 rabbits, one died two weeks after receiving the injection, during a minor epidemic of enteritis, and revealed no sign of tuberculosis, while the other died

in six weeks of extensive tuberculosis. Cultures of the original chicken liver and spleen on various mediums yielded acid-fast bacilli which on injection into chickens killed them with typical tuberculosis.

Many other chickens died during the course of the experiments. Perhaps the most common cause of death was leukemia or a leukemoid reaction. Such chickens did not acquire a positive reaction to tuberculin, although occasionally a slight edematous swelling occurred at the test site. They did not lose much weight, and at autopsy the gross observations were not those of typical tuberculosis. Histologic examination revealed the nature of the disease. There was an absence of stainable acid-fast bacteria in such lesions, cultures for acid-fast organisms were negative and in several passage experiments no tuberculosis was produced. Furthermore such leukemoid reactions occurred in the control groups of chickens, both those given and those not given injections.

Another lesion worthy of special mention which was encountered 4 times was a granuloma of the wall of the gastro-intestinal tract, usually in the cecum. These masses grossly resembled one described by L'Esperance [6a] as tuberculous. Microscopically, however, they showed varying amounts of new granulation tissue and fibrous connective tissue. There were areas of massive necrosis and also smaller necrotic foci, at the periphery of which there was sometimes a marked giant cell reaction. The chickens producing the granulomas lost much weight. They had persistently negative reactions to tuberculin. No acid-fast bacteria were ever seen in multiple stained sections and no growth of acid-fast organisms was recovered in cultures. Passage experiments failed to produce tuberculosis in the various species of animals used. Two chickens in which such tumors developed were *controls not given injections;* another was a control given an injection of a suspension of lymphosarcomatous tissue, and the fourth was a chicken used in a passage experiment in which a suspension of tissue from a leukemic chicken was injected. These lesions are therefore considered to be nontuberculous.

Lesions of still another type were encountered in 3 chickens. These consisted of firm, grayish-yellow, discrete but unencapsulated nodules in the liver, measuring from 4 to 10 mm. in diameter. On histologic examination the nodules were seen to be made up of many types of cells, among which small and large mononuclear cells predominated. There were numerous cells resembling myelocytes, as well as some large mononuclear giant cells. Cells with a granular, eosinophilic cytoplasm were numerous. Cells of the type of the plasma cell were also present. All these cells were supported in a reticular framework which resembled that of the original liver (fig. 1). In addition to these features common to all, one nodule showed several focal accumulations of densely packed cells with small round and oval nuclei with an even chromatin pattern and a very eosinophilic, finely granular, moderately abundant cytoplasm.

Immediately surrounding these foci were found rings of endothelioid giant cells with clusters of pale nuclei and indefinitely outlined cytoplasm (fig. 2).

As far as one can determine from an examination of photomicrographs, these lesions show a remarkable resemblance to those illustrated by L'Esperance.[6a] However, I do not consider them tuberculous for the following reasons: No acid-fast organisms were demonstrable in them. The chickens on repeated tests never gave a positive reaction to tuberculin. Moreover, two of the lesions occurred in *controls that had not had injections.* The third was found in an apparently healthy

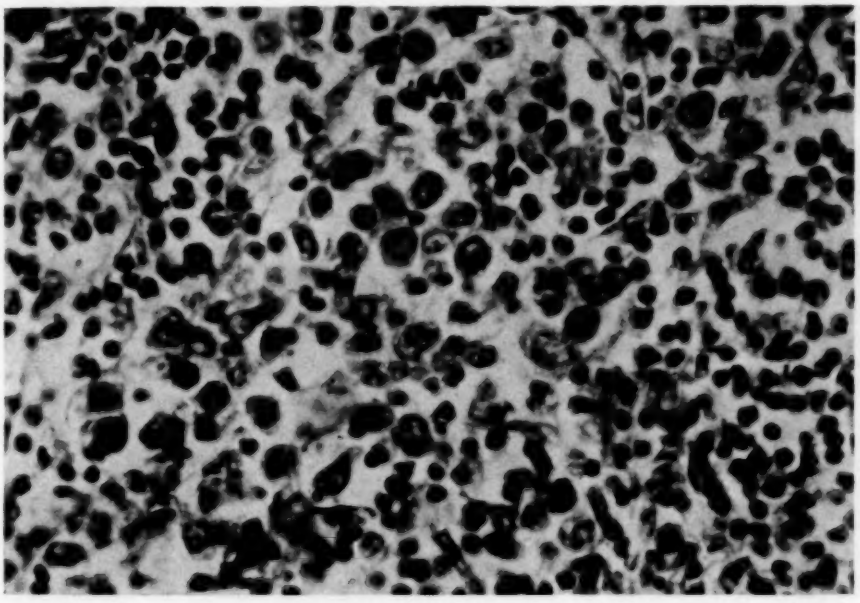

Fig. 1.—High power photomicrograph showing the types of cells found in the hepatic nodules. × 1450.

chicken killed nine months after it had received an injection of a suspension of tissue from the patient in case 13, one of Hodgkin's disease. The other 2 chickens given injections of the same material and examined post mortem at the same time showed no disease. None of the lesions of this type showed any tendency to dissemination or to production of a fatal disease. Unfortunately, no passage experiments were performed with these lesions.

The other chickens that died before the termination of the experimental period showed a variety of lesions. They failed to show positive reactions to tuberculin or evidence of tuberculosis. Five chickens that received injections of suspensions of tissue from 2 persons with tuber-

culous adenitis presented no sign of tuberculosis. Likewise those given injections of tissues from persons with leukemia and lymphosarcoma did not become tuberculous.

Of the 24 guinea-pigs into which injections or transplantations of Hodgkin's tissues were made, only 1 contracted tuberculosis. This animal (G-P47) presented enlargement of the inguinal lymph nodes on the side of the injection and when tested four months later had a positive reaction to human tuberculin and a negative reaction to avian tuberculin. The original lymph node obtained for biopsy from the cervical region of a man 21 years of age showed no microscopic evidence

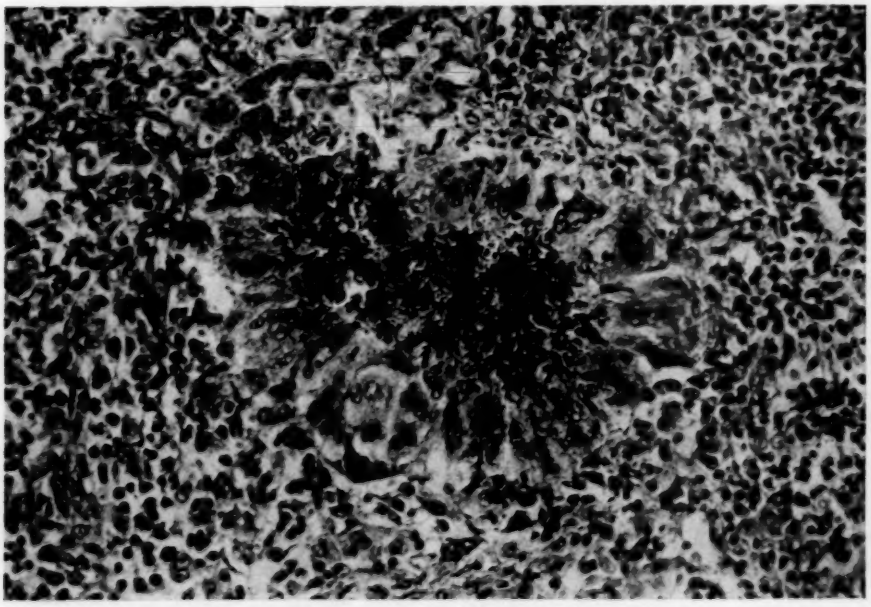

Fig. 2.—Type of lesion, resembling a tubercle, found in the hepatic nodule shown in figure 1. This is considered nontuberculous. × 500.

of tuberculosis (case 17). The animal died six and one half months after it received the injection, with extensive tuberculosis of the lungs, liver, spleen and lymph nodes. The other guinea-pig and the 2 chickens that received injections of the same material never showed positive reactions to tuberculin and at the termination of the experiment showed no evidence of tuberculosis.

Two guinea-pigs that received injections of a suspension of tissue from one of the control patients with tuberculous adenitis died of tuberculosis. Of 13 guinea-pigs that received injections of material from 3 persons with lymphosarcoma and 3 with leukemia, 1 developed tuberculosis (case 3). This animal (G-P17) died of marked generalized

tuberculosis five months after tissue from a retroperitoneal lymph node had been engrafted into it. The node showed the histologic picture of a reticulum cell type of lymphosarcoma. No special significance was attributed to this observation since the injection of nontuberculous lymph node tissue from this location not infrequently produces tuberculosis in animals.

No rabbit, not even the 2 given injections of the material from the 2 patients with tuberculosis, contracted tuberculosis during the experiments. Seven dogs received intracerebral injections of suspensions of tissue from persons with Hodgkin's disease and one, of a suspension of lymphosarcomatous tissue, without showing evidence of tuberculosis. Of the mice that became tuberculous during the experiments, both had received injections of material from a person with tuberculous adenitis.

Because of the success of Nungester [18] in enhancing the virulence of bacteria by suspending them in sterile gastric mucin, this method was tried in 1 case of Hodgkin's disease. One dog and 2 guinea-pigs failed to acquire tuberculosis after being given injections of the diseased tissue suspended in mucin.

EVIDENCE FROM CULTURES

Cultural studies were undertaken, not primarily to determine the bacterial flora of the tissues from the patients with Hodgkin's disease, but to demonstrate acid-fast organisms if they were present. Many of the reported bacteriologic studies on lymphogranulomatous tissues antedate the development of cultural methods and procedures which today are highly recommended for the isolation of acid-fast bacteria. Thus the cultural studies served as a control of the injections and permitted application of some of the reputedly superior methods for the isolation of tubercle bacilli.

An attempt was also made to repeat the observations of Busni.[19] She reported that from tissues showing Hodgkin's disease she was able regularly to grow bacteria which, when examined at from twelve to twenty-four hours, were acid-fast and resembled Koch's bacillus. After another period of from twelve to twenty-four hours they appeared as small nonacid-fast cocci. After further incubation, at a time when macroscopic growth was not yet evident, they resembled masses of staphylococci. Special procedures were devised to make analogous observations on cultures concerned here.

Experimental Procedure.—Fragments of diseased spleen and lymph node tissues were inoculated into culture mediums as soon as possible after they were obtained for biopsy or at autopsy. This was usually within a few hours after their removal.

18. Nungester, W. J.: Proc. Soc. Exper. Biol. & Med. **30**:120, 1932.
19. Busni, N.: Virchows Arch. f. path. Anat. **268**:614, 1928.

Thin, wafer-like slices or macerated tissues were transferred to the surface of solid mediums in culture tubes. In some cases contamination was suspected and the tissues were treated with 6 per cent sulphuric acid, 5 per cent ovalic acid or 3 per cent acetic acid for thirty minutes or more before inoculation. The mediums used were Sweany's [20] veal, cream, milk, egg, medium, Corper's potato [21] and Herrold's egg yolk medium.[22] The latter was modified in a few instances by the addition of 5 per cent glycerin. Loeffler's serum, blood agar and Petroff's egg medium were also used at various times. Numerous tubes were inoculated with material from each case. Incubation was continued for periods up to nine months.

It is generally recognized that partial carbon dioxide tensions are superior for the isolation of some acid-fast bacteria. Accordingly some of the culture tubes were incubated in 10 per cent carbon dioxide tensions at 37 C. Since lower temperatures have been advocated as advantageous for certain strains, some tubes were kept at room temperature. The criteria for sterility have been modified by the pioneer work of Hauduroy [23] on serial plate transfers. With certain specimens that appeared sterile after prolonged incubation his technic was employed for periods up to twenty days before the tubes were discarded as sterile. In an attempt to repeat the observations of Busni, examinations of apparently sterile cultures were made at twenty-four hour intervals by grasping the implanted tissue in the culture tubes with sterile forceps, touching the surface which was in contact with the culture medium to the surface of a sterile glass slide, and then examining the slide preparations after staining them by the Ziehl-Neelsen and Gram methods.

Results.—No cultures of definitely acid-fast bacilli were obtained by these methods from tissues in 11 cases of Hodgkin's disease. Although the mediums were not especially suitable for the growth of the diphtheroids so frequently recovered by many investigators, bacteria of this type were grown in 4 cases, and other common bacteria usually considered to be contaminants were grown occasionally. In 2 cases the culture tubes remained sterile.

In only 2 instances were observations made resembling those reported by Busni. From a cervical lymph node removed for biopsy in a case of Hodgkin's lymphogranulomatosis, implanted on modified Herrold medium and incubated in 10 per cent carbon dioxide tension, small nonacid-fast bacilli of medium size appeared on the impression slide preparations. Observation of these organisms revealed that most of the body was gram-negative but that it contained from one to four, usually two, gram-positive granules of a diameter equal to that of the bacillus. The organisms containing four granules appeared to be short chains of streptococci. When only two granules were present the appearance suggested a diplococcus. After another forty-eight hours of incubation rather small, slightly beaded bacilli resembling diphtheroids, but with a tendency to be acid-fast, were numerous. Macroscopic evidence

20. Sweany, H. C., and Evanoff, M.: Am. Rev. Tuberc. **18**:661, 1928.
21. Corper, H. J.: J. A. M. A. **91**:371, 1928.
22. Herrold, R. D.: J. Infect. Dis. **48**:236, 1931.
23. Hauduroy: Compt. rend. Soc. de biol. **97**:1392, 1927.

of growth first appeared on the ninth day, and an organism resembling a diphtheroid, without any tendency to be acid-fast, slowly grew out.

In another case the sterile slide impressions prepared after twenty-four hours of incubation of tissue secured for biopsy from a cervical lymph node in a case of Hodgkin's disease showed clusters of gram-positive coccus-like organisms. These, however, failed to become grossly visible, and although the rapid serial plate technic was used, no bacterial colonies were ever obtained.

Five controls consisting of tissues from 3 patients with lymphosarcoma and 2 with leukemia yielded no significant organisms. No acid-fast bacteria were grown from them. Diphtheroids were grown in 1 case and staphylococci were grown in 2.

COMMENT

In this intensive search for tubercle bacilli in tissues from patients with Hodgkin's disease by inoculation of the tissues into a variety of species of animals and by cultural methods little evidence of such organisms was found. No acid-fast strains resembling tubercle bacilli were grown by cultural methods, and inoculation of material from fifteen patients with Hodgkin's disease into animals gave tuberculosis in only 1 guinea-pig and 1 chicken. In the latter animal a spontaneous tuberculous infection was not ruled out. In neither of these cases were other animals infected by injections of the same material.

If the results of Dolgopol [24] showing that chickens are insusceptible to infection by the human type of tubercle bacillus are accepted—and this observation is confirmed in the 2 control cases of tuberculous adenitis used in this series—it becomes apparent that the 1 chicken that contracted tuberculosis in these experiments was infected with tubercle bacilli probably of avian type. This is substantiated by the results of injection of infected tissues and of cultures of acid-fast bacilli obtained from this chicken into other chickens.

One important factor in the propagation of tuberculosis in animals is the size of the infecting dose. This was borne in mind throughout the investigation. Consequently, in many experiments, large amounts of the diseased tissues were macerated and thick suspensions were prepared. Of these, large amounts were injected (see table 1). Nevertheless the incidence of infection remained low.

Another important factor is the resistance of the test animals. Overcrowding, poor ventilation, dark quarters, undernourishment and vitamin deficiencies lead to a higher incidence of infection. Among my experimental animals the chickens alone were subjected to some of these adverse conditions. Still they failed to present tuberculosis. This leads to the belief that acid-fast organisms pathogenic for chickens were

24. Dolgopol, V. B.: J. Infect. Dis. **49**:216, 1931.

extremely infrequent in, or entirely absent from, the tissues of the patients with typical Hodgkin's disease whom I studied.

Ewing [25] emphasized the factor of duration of time in the production of tuberculosis with such tissues. Although many of my experiments were allowed to continue for over one year there was no increased incidence of infection.

The incidence of tuberculous infection in guinea-pigs in this series was also smaller than that reported by some investigators. One guinea-pig of the 24 given injections of the tissues showing Hodgkin's disease was infected. This incidence closely approaches that reported by Twort [26] and by Gordon.[27] The latter produced tuberculosis in 3 of 40 guinea-pigs subjected to injection.

The diphtheroids so frequently grown in cultures of tissues from persons with Hodgkin's disease who have not been treated become increasingly difficult to recover from tissues irradiated by roentgen rays. It is not known whether the destruction by irradiation also applies to the tubercle bacillus. To avoid this possibility, many tissues that had never been irradiated by roentgen rays were used. This apparently had no influence on the final result.

During the examination of smears from diseased tissues stained by the Ziehl-Neelsen method a phenomenon was noticed which at first was confusing. Acid-fast granules and débris suggestive of degenerated bodies of tubercle bacilli were often seen. In sections of these same tissues stained by the Cooper method the nature of the acid-fast materials became apparent. A restudy of the original smears then supported the opinion that they were either granules from eosinophilic leukocytes or débris resulting from the destruction of red blood cells. The cytoplasm of the latter was found to be unusually tenacious for the fuchsin stain.

SUMMARY

Diseased splenic and lymph node tissues from 15 patients with Hodgkin's disease (lymphogranulomatosis) together with control diseased tissues from 8 patients with other lymphomas were investigated (1) for the ability of the diseased tissue to produce tuberculosis in chickens, guinea-pigs, rabbits, dogs and mice, (2) for the disease-producing capacity of these tissues as grafts, and (3) for the presence of tubercle bacilli or atypical acid-fast bacteria in these same tissues, special cultural methods being used. The diseased tissues from the 23 patients were

25. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 407.

26. Twort, C. C.: J. Path. & Bact. **33**:539, 1930.

27. Gordon, M. H., in Rose Research on Lymphadenoma, Bristol, John Wright & Sons, Ltd., 1932.

injected or transplanted into 199 animals of the species mentioned. An additional group of 23 chickens that were not given injections served as a control of environmental factors, especially of the occurrence of spontaneous tuberculosis. A group of 8 dogs received intracerebral injections. The animals were allowed to survive for periods varying from nine to thirteen months. The criteria used for the diagiosis of tuberculosis in the animals following injection were: (1) the acquisition of a positive reaction to tuberculin, (2) the gross and microscopic morphologic structure of tuberculous lesions, (3) the presence of stainable acid-fast bacilli in suspicious lesions, (4) the growth of acid-fast bacilli from such lesions on culture mediums and (5) the production of tuberculosis in animals in passage experiments.

In the entire group of animals given injections of diseased human tissues, tuberculosis occurred in 1 chicken following injection of material from a patient with Hodgkin's disease, 1 guinea-pig following injection of tissue from a patient with Hodgkin's disease, and 1 guinea-pig following injections of lymphosarcomatous tissue. In the infected chicken a spontaneous infection was not ruled out. In passage experiments with tissues from these infected animals tuberculosis was again produced.

Numerous lesions in diseased chickens superficially suggesting tuberculosis were considered nontuberculous because they did not definitely satisfy *any* of the five criteria previously laid down.

No evidence was found that the diseased human tissues were transplantable or that they were capable of inducing in animals lesions with a similar histologic structure.

No strains of acid-fast bacteria were grown from these diseased human tissues by modern cultural methods. Likewise the occurrence of acid-fast forms of bacteria reported to exist as a transient phenomenon early in the cultures of these tissues was not confirmed.

Avian tubercle bacilli detectable by the methods used were apparently not present in the tissues of the 15 patients with Hodgkin's disease.

THE PROLIFERATIVE REACTION OF GUINEA-PIG SKIN TO SULPHYDRYL AND ITS RELATION TO NEOPLASIA

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PHILADELPHIA

Experiments for another purpose involved the application of sulphydryl compounds to the skin of guinea-pigs. Since no results of a study of the skin of guinea-pigs after application of these compounds have been published, we record the results of our study.

PROCEDURE

Benzyl mercaptan in a concentration of 5 per cent in alcohol was applied three times weekly for two weeks to the midscapular region of twelve guinea-pigs. Sections of the skin were removed at weekly intervals. The *p*-thiocresol in a concentration of 0.5 per cent in hydrous wool fat was applied to the same animals three times weekly. The hair over the region of application was kept closely cropped. Sections of skin were removed, fixed in Sousa's solution,[1] embedded in paraffin, cut at 3 microns, and stained with hematoxylin and eosin and with iron-hematoxylin. Sections were taken at intervals of two or three weeks over a period of three months. As controls, the skins of untreated guinea-pigs were used.

RESULTS

As in rats and mice [1a] so in guinea-pigs the skin becomes palpably thickened from ten days to two weeks onward.

The normal skin of guinea-pigs differs from that of mice in the direction of slightly more differentiation and organization. The epithelium is from 2 to 4 cells thick. There is no special regularity except in spots. There is no clear, unbroken basement membrane, and few local groups of cells with protoplasmic bridges are present.

As early as after the second application of benzyl mercaptan, changes are recognizable. Since they are identical with those occurring

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From the Lankenau Hospital Research Institute.

This investigation was aided by a grant from a group of trustees of the Lankenau Hospital.

1. Sousa's solution is made as follows: Boil together distilled water, 700 cc., mercuric chloride, 45 Gm., and sodium chloride, 5 Gm. When cool, add 20 per cent trichloracetic acid, 100 cc., a diluted solution of formaldehyde U. S. P. (1:40), 200 cc., and glacial acetic acid, 25 cc.

1a. Reimann, S. P.: Protoplasma **10**:82, 1930.

in rat and mouse skins, which were completely described in previous communications,[2] merely a brief résumé will be given.

A clear, unbroken basement membrane appears. The cells of the basal layer become oriented vertically and are present as a very definite layer. Toward the surface from these there appears a definite layer of

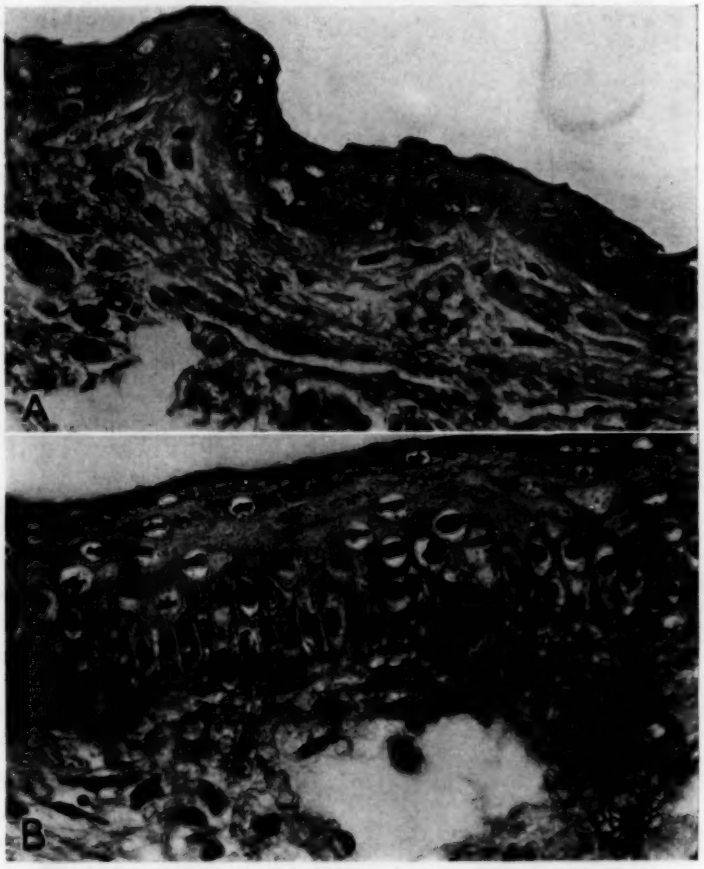

Fig. 1.—*A*, control, untreated skin of guinea-pig; × 370. *B*, skin of guinea-pig after 5 per cent benzyl mercaptan in alcohol had been applied three times weekly for two weeks, then 0.5 per cent *p*-thiocresol in hydrous wool fat three times weekly for three weeks; × 370.

spinous cells, and beyond them a definite layer of pigmented cells. Search of the untreated skin resulted in the discovery of two mitoses over a length of about 2 cm. Over the same length in the treated skin there were found eight, ten, eleven, nine and fifteen mitoses in as many sec-

2. Hammett, F. S.: Protoplasma **13**:331, 1931.

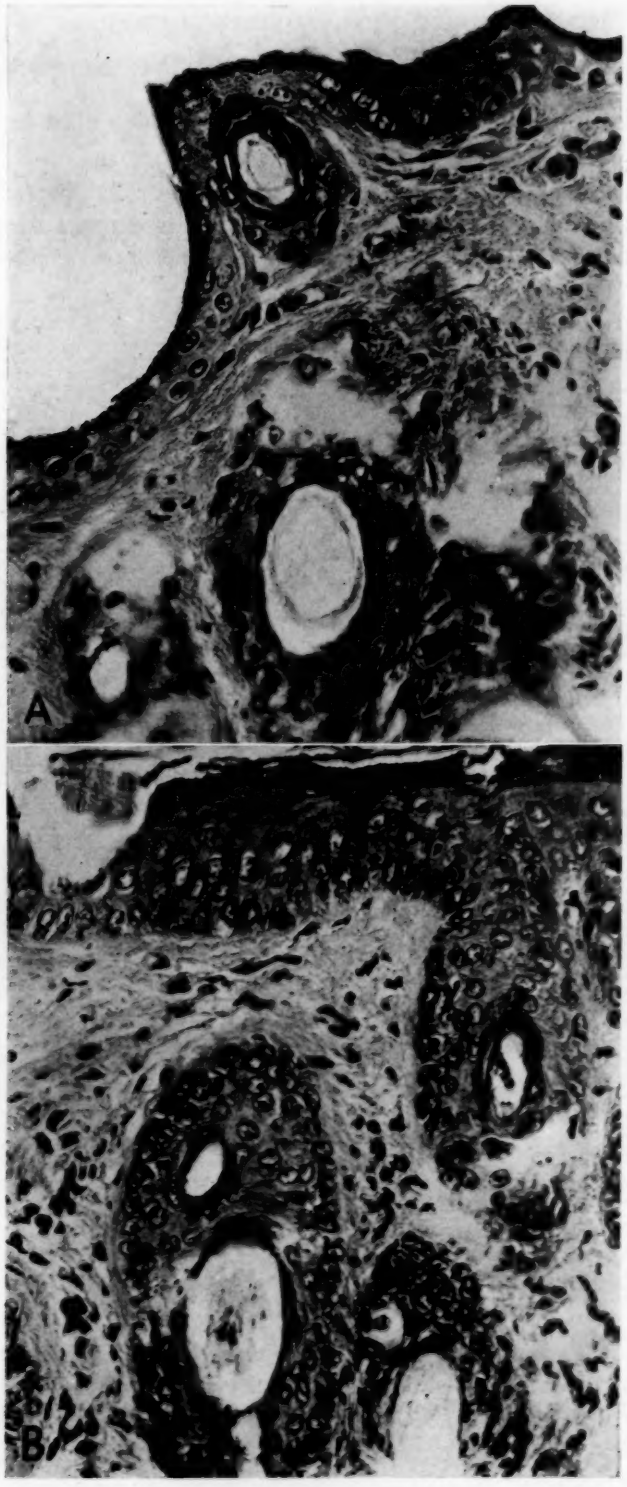

Fig. 2.—*A*, control, untreated skin of guinea-pig to show hair follicles; × 370. *B*, skin of guinea-pig after 5 per cent benzyl mercaptan in alcohol had been applied three times weekly for two weeks; × 370.

tions over a length of about 2 cm. The mitoses, whether in treated or untreated skin, were all in the basal layer.

These changes, as stated, are apparent at the end of two or three applications. At the end of from twelve to fifteen applications they apparently reach their height and remain in about the same degree for the remainder of the three months' experimental period.

COMMENT

The development of any organism, organ or tissue which is accomplished by the multiplication of cells occurs by the route of three separate processes occurring in these cells, namely, multiplication, differentiation and organization. These processes are separate and distinct manifestations of the potency of protoplasm. Biologically they serve different ends, and one or the other can be thrown out of "gear" separately from the others.[3] On the other hand, they are also related, for obviously cells cannot differentiate and organize if they are not there, i. e., they must proliferate. Conversely, if they do proliferate, they must, in order to develop normally, differentiate and organize in tune to the genus, species, individual, organ and tissue in which they are present.

In a previous communication, Hammett,[2] analyzing the phenomena in the skin of the rat and mouse, concluded that the more rapid the proliferation the more rapid the differentiation and organization. In addition there emerged the yet more important conclusion that increasing the rate of proliferation not only increased the rate of differentiation and organization, but also increased their degrees, from which it was concluded in relation to neoplasia [4] that when cells proliferate at rates greater than normal or when more cells are produced than are normal for the part, the end-result is not a neoplasm, provided that the potencies of the cells, i. e., their internal composition, remain normal. The next logical statement in regard to neoplasia is: Neoplastic cells have altered potencies of differentiation and organization.

These bald statements are taken from previous communications [5] in which results in additional species are recorded. To which are added the experimental results from the use not only of sulphydryl but also of a partially oxidized derivative, i. e., the sulphur equilibrium, as originally described and experiments planned by Hammett and Hammett.[6] A

3. Needham, J.: Chemical Embryology, New York, The Macmillan Company, 1931, vol. 3, p. 1650.

4. Reimann, S. P.: Am. J. Cancer **15**:2149, 1931.

5. Reimann.[4] (*a*) Hammett, F. S., and Hammett, D. W.: Protoplasma **17**: 321, 1932. (*b*) Reimann, S. P.: Arch. Path. **15**:675, 1933.

6. Hammett, F. S., and Hammett, D. W.: Protoplasma **15**:59, 1932; **16**:253, 1932; **19**:161, 1933. Hammett, F. S.: ibid. **19**:510, 1933.

tentative definition of a neoplasm was attempted on the basis of these results.[5b]

Some authors call this internal change of potency of neoplastic cells "somatic mutation," with which we are in agreement if, and provided that, a strict definition is given of what is meant by "somatic mutation." [7] Otherwise biologists must accept that tar, dibenzanthracene, indeed all of the chronic irritants in general which cause or are followed by cancer are producers of mutation. This they may not be willing to do (as yet, if ever) in view of the difficulties experienced in producing mutations (acceptable to them) by temperature changes, etc., until Muller succeeded by means of the x-rays.[8]

This being the case, we shall continue to say that neoplastic cells have altered potencies of differentiation and organization until later agreement is reached as to definitions. Also, for the reasons given in a previous paper, which are confirmed by the results in another animal, described in this paper, we shall continue to define a neoplasm as follows: *It is a mass of cells which arise from and continue to proliferate within an organism as a result of and in direct proportion to their degree of internal qualitative differences from the other cells of the organism with respect to the potencies of differentiation and organization particularly.*[5b]

SUMMARY AND CONCLUSIONS

Another animal, namely the guinea-pig, has been added to the growing list of organisms which have been proved responsive in their rates of cell division to the sulphydryl group. As in rats and mice, when the sulphydryl group is applied to the skin of guinea-pigs there results an increase in the rate of cell division followed secondarily by an increase in the degree of cell differentiation and organization. The same implications and conclusions both in regard to general biologic principles and in regard to neoplasia are again justified from the material in these animals. The reader is referred to these papers for further details.

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7. Bauer, K. H.: Mutationstheorie der Geschwulst-Entstehung, Berlin, Julius Springer, 1928. Curtis, M. R.; Dunning, W. F., and Bullock, F. D.: Science **77**:175, 1933; Am. J. Cancer **17**:894, 1933. Kostoff, D.: Protoplasma **20**:440, 1933; Editorial, J. A. M. A. **102**:214, 1934.

8. Hanson, F. B.: Physiol. Rev. **13**:466, 1933.

METAMORPHOSIS OF METASTRONGYLUS LARVAE AND MESENTERIC LYMPH GLANDS

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Lymph glands have generally been considered to be strongholds against infections of any kind. No parasite was known to breed exclusively in these glands at any point of its life cycle. Recently it has been found, however, that this theory does not apply to Metastrongylus.[1a, b] Its metamorphosis from larvae of the infestive stage into sexual larvae takes place exclusively in the mesenteric lymph glands.

This invasion is, of course, destructive to the involved glands in varying degrees according to the numbers of migrating parasites. The cases here presented are the result of extremely heavy infestations under the experimental conditions previously described.[1a] A similar behavior has been found in other lungworms, as for instance in Dictyocaulus of sheep.[1c] Metastrongylus, however, was selected for these studies owing to the peculiar structure of the lymphatic glands of swine which enables the worker to locate the migrating larvae in a manner not possible in the glands of sheep or any other domestic animal. The trabeculae in the lymph glands of swine are highly developed, forming extensive layers of connective tissue between the follicles. Furthermore, they enclose broad lymph vessels which are discharged into the lymph sinus,[2] a fact essential in the course of the present investigation.

Since it was found that the infestive stage of Metastrongylus develops in an intermediate host,[3] it was possible to approach a solution of the much discussed problem of the development of lungworms in the vertebrate host.

Histologic studies soon revealed lesions, connected with the migrating nematodes, on the wall of the intestine. Inconspicuous infiltrations of eosinophilic blood cells have been encountered in the stroma of the villi, in the mucosa, in the submucosa, rarely in the muscularis around vessels and even in the subserosa. They were, however, more numerous

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From the Hooper Foundation for Medical Research, University of California.

1. (*a*) Hobmaier, A., and Hobmaier, M.: München. tierärztl. Wchnschr. **80**:365, 1929; (*b*) **80**:433, 1929; (*c*) **80**:621, 1929.

2. Trautmann, A.: Ztschr. f. Anat. u. Entwcklngsgesch. **78**:733, 1926.

3. Hobmaier, A., and Hobmaier, M.; [1a] von Schuckmann, W., and Zunker, M.: Ztschr. f. Infektionskr. **38**:353, 1930. Schwartz, B., and Alicata, J. E.: Parasitology **18**:21, 1931.

in the region of the colon and cecum than in other parts of the intestine. Scattered cells of that type or aggregations of them have been observed in those regions. Furthermore, the local eosinophilic infiltration was strongly marked on the mesentery in the vicinity of lymphatic vessels between the intestine and lymph glands.

Practically every lymph gland of the intestine has been found invaded by the nematodes, owing to the extremely large numbers of larvae administered to the animals. The larvae, however, varied greatly in number in different sections of the intestine. They were most frequently found in the lymph glands of the colon and cecum and in those of their vicinity. Their numbers decreased steadily toward the rectum and toward the stomach. No larvae could be detected in any lymph gland not directly connected with the digestive tract.

So far as pathologic changes are concerned, two phases may be distinguished. The acute stage lasts about six days, beginning with the invasion of the glands by the migrating larvae and ending with their emigration. The chronic phase or stage of reparation, on the other hand, is to be noted following their emigration.

During the first period the involved glands appear enlarged. They present a spherical or finger-like shape. The capsule is extended. No hemorrhages of any significance are visible. On sections of the glands the tissue is seen protruding and rich in fluid.

Histologic investigations showed the larvae accumulated in the lymphatics of the trabeculae. It seems that ordinarily the larvae of Metastrongylus do not enter the marginal sinus before they have grown into the sexual stages. The pictures favor the belief that most of the infestive larvae are arrested in the lymphatics of the trabeculae where the larger lymphatics lose width near the marginal sinus. In other words, an embolization takes place. As soon, however, as the larvae have grown from the infestive into the sexual stages, an exsheathment follows, and they continue their way into the marginal sinus and from there pass in the prescribed way of the lymphatics until they become finally arrested for a second time by embolization in the capillaries of the pulmonary artery. It need hardly be mentioned that studies on structural features of the larvae require fresh preparations; meanwhile, histologic investigations are required in topographic studies concerning the exact localizations of the larvae. Feeding of a large number of larvae makes it easy to recover many of them in lymphatics of the trabeculae. The disadvantage of this method, however, is that the anatomic structure of the glands may become endangered and as a consequence at least some of the larvae may take an abnormal route of migration.

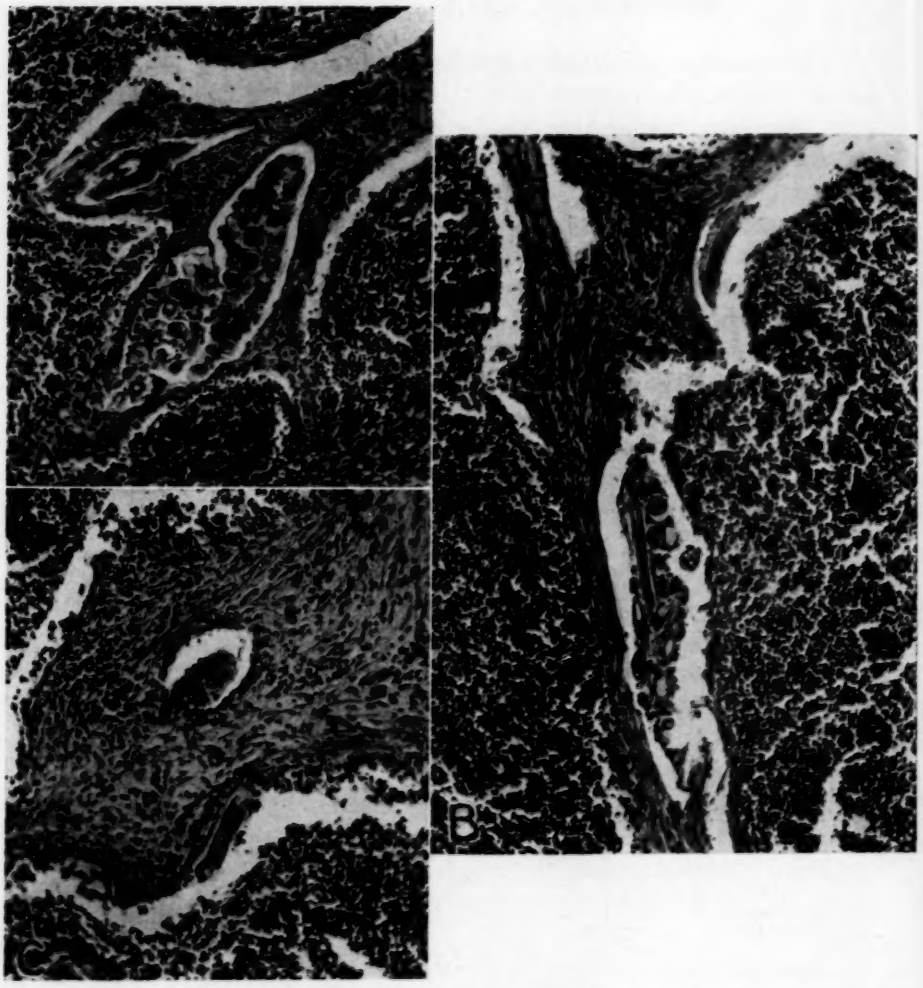
The lumens of the invaded lymphatic vessels appear distended. The larvae may be found curled up in the vessels, varying greatly in numbers (fig. A). No peculiar reaction takes place at this time so far as the walls of these vessels are concerned. Only a few lymphocytes and some eosinophils may be found between and near the larvae. A paucity of coagulated plasma may be seen occasionally. Some of the larvae show different stages of molting. The trabeculae themselves appear enlarged. Their normal structure is supplanted by a reticulum of angioblasts and fibroblasts presenting the picture of a young granulating connective tissue. Eosinophilia is present throughout the trabeculae. Most frequently the lymph vessels are surrounded by these cells. Occasionally ecdysis may be observed on larvae enclosed in lymph vessels bordering the lymph sinus. It seems that the wall of the vessel attenuated by the pressure of the growing larva bursts under the stronger movements of the exsheathed larva, dismissing it into the marginal sinus (fig. B).

No eosinophilia is seen in the lymph nodes. Their center is often poor in lymphocytes. Their peripheral region borders without sharp lines the marginal sinus. The latter presents the usual picture of sinusal catarrh. Its reticulum is completely filled with a superfluity of lymphocytes and eosinophils. In several places sections of well developed (sexual) larvae may be found. Occasionally small foci, consisting of the remnants of a nematode larva surrounded by a mass of eosinophils and lymphocytes, have been encountered.

During the second phase, the period after the larvae have left the lymph glands, a reparation of the disintegrated tissues may be seen in progress. Macroscopically the glands are still larger than usual. However, they now appear harder than normal glands and more strongly attached to the surrounding tissue.

The microscopic pictures of the affected glands vary greatly in different sections. In some places the normal structure is completely lost; in other parts there is little alteration beside the eosinophilic infiltration. The great variety of the microscopic aspect due to the migrating larvae may be easily understood, considering the irritation of the connective tissue with its vessels which are present in the trabeculae and in the stroma of the glands. As often seen in pathologic changes, the response to the injury is not confined to a limited and what seems to be an adequate reparation, but an excessive granulation precedes the definite repair. An abundance of vascularization generally produces an abundance of granulation. These conditions are fulfilled to a high degree in the lymph glands. Consequently the reaction to trauma is strong in these glands.

The angioblasts and the fibroblasts of the trabeculae grow into the marginal sinus, disregarding the anatomic border lines. The lymphatic



Mesenteric lymph gland showing Metastrongylus larvae. *A*, a mesenteric lymph gland. Two lymphatics are visible in the trabecula. The lymphatic vessel above contains a longitudinal section of a Metastrongylus larva. In addition to that, a small amount of coagulated plasma is visible. The lymphatic vessel below shows extreme dilatation. The trabecula itself is attenuated in its vicinity. The wall of the vessel is ready to open into the marginal sinus. The lumen of the vessel is filled with segments of the larvae embedded in coagulated plasma intermingled with eosinophils. *B*, the lower part of the trabecula is attenuated. A number of longitudinal and transverse sections of Metastrongylus larvae may be seen in the lymphatic vessel. The wall bordering the marginal sinus is ruptured, and the larvae are about to invade this region. In the upper right corner of the marginal sinus a longitudinal section of a sexual larva already liberated is visible. *C*, enlarged trabecula consisting chiefly of angioblasts and fibroblasts intermingled with eosinophils. The wall of the lymphatic vessel in its middle shows an eosinophilic infiltration and the early repair of the wall following the emigration of the larvae. A longitudinal section of a newly liberated sexual larva of Metastrongylus may be seen in the marginal sinus below.

cells, on the other hand, invade the spaces left between the granulating tissue. The lymph nodes stimulated to high activity discharge large quantities of lymphocytes into the environment, thus overflowing the region of the marginal sinus and disarranging the entire structure of the lymphatic gland. Under these circumstances the trabeculae are sometimes reduced to a few angioblasts and fibroblasts; sometimes they appear considerably enlarged and merge indistinctly into the nearby tissues.

In other parts of the glands the normal structure may be easily recognized. The trabeculae may be seen rebuilding their fibrous structure. The border lines between lymph nodes and trabeculae may be clearly marked. The lymph sinus may present the normal appearance. In other cases, many capillaries are seen crossing this interspace, accompanied in places by strains of connective tissue. A paucity of lymphocytes is apparent only in the meshes left between the capillaries and the connective tissue. It is noteworthy that the eosinophilia still endures in the course of these changes.

Small quantities of coagulated plasma may sometimes be found in lymphatic vessels invaded by larvae. These small thrombi finally become organized with a limited number of lymphocytes, white blood cells and eosinophils. They seemingly immigrate through the wall of the affected vessels involving this part of the wall in the process of reparation, as shown in figure *C*.

It is generally known that young swine are more readily affected by lungworm disease than older ones. The normal anatomic and the pathologic changes in the tissues of the host during life, and especially the changes taking place in mesenteric lymphatic glands, may be at least partially responsible for the higher resistance, rather than biologic processes of immunity.

Since the discovery of Stewart concerning the migration of Ascaris in blood vessels it has been suspected that larvae of lungworms may act in a similar way. In accordance with that theory the migrating larvae would be found passing through the liver. The tissues of the lungs, on the other hand, would show, besides exsheathed larvae of the infestive stage, ensheathed sexual larvae during the first days after infection.

No macroscopic changes could be observed in the liver. Large areas of the liver have been investigated microscopically in fresh preparations, but without success. Microscopic slides of fixed material taken from about one hundred different points showed changes due to a nematode's having recently migrated in the tissue in three specimens only. The larvae themselves, already in a state of decomposition, were situated on the periphery of the lobules. A small accumulation of round cells and eosinophils surrounded the dead nematodes. The same cells were found

in the vicinity and especially in the nearby interlobular connective tissue. It was, of course, not possible to determine whether these larvae were originally a part of the larvae fed to the animal, though it is probable. If this is true, their peripheral localization appears to indicate that the larvae were already too large to pass through the capillaries of the liver.

Investigations of similar material conducted one and two months later still showed a local eosinophilic infiltration, where larvae had previously perished. No production of fibrous tissue in any considerable amount had taken place. No macroscopic changes were seen. There is apparently no connection between lungworm disease and parasitic interstitial hepatitis in swine as claimed by different workers.

An extended search in the lungs during the time of immigration resulted in the detection of a few exsheathed larvae of the infestive stage. No ensheathed larvae of the sexual forms could ever be found, but exsheathed sexual larvae were present in exceedingly large numbers. No molting larvae were found in the lungs, but it was possible to observe on fixed material a few tubercles embedded in the region of the alveoli. They consisted of the débris of a minute nematode larva. An aggregation of round cells, eosinophils and of one or two giant cells surrounded them. These tubercles may have been the product of a biologic reaction against erratic infestive larvae, which were apparently not yet sufficiently developed to live and to grow in this environment.

CONCLUSION

The present study corroborates the previous statement of A. Hobmaier and myself that the infestive larvae of Metastrongylus must invade the mesenteric lymphatic glands of the vertebrate host to grow there into sexual larvae and that they do not enter the tributaries of the portal vein as a part of their regular life cycle.

The pathologic changes observed in the invaded lymph glands may be explained as the result of the trauma inflicted by the embolization of the larvae into the lymphatics, by the dilatation and occlusion of these vessels during the development of sexual larvae, and by the disarrangement of anatomic structures caused by their emigration.

AN ANALYSIS OF CORONER'S STATISTICS FROM COOK COUNTY (CHICAGO), ILLINOIS

WITH A PATHOLOGIC REVIEW OF THE CAUSES OF DEATH

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INTRODUCTION

The present study is a statistical survey of all deaths investigated and passed on by the coroner's staff of Cook County, Ill., within the four years of a single term of office, from November, 1928, to November, 1932.

The question of the coroner system versus the medical examiner system is outside the scope of this study, but significant references follow.[1]

This period was taken as representing exceptional conditions for efficient functioning of the coroner's medical personnel. It was felt that under such conditions the general trend of the statistical data of the coroner's system is similar to that of a more ideal system.

The coroner's physicians were chosen from a group qualified by previous pathologic training. They were selected by an advisory board appointed by the coroner, composed of professors of pathology of the four major medical schools of Chicago. This method of selection secured physicians who were not only adequately trained but free from political influence and demands. Furthermore, the wide experience of the advisory board was made freely available in the organization of field work and in the solution of pathologic and medicolegal problems.

The importance of an efficient unit of trained examining physicians as an aid to the state in deaths involving medicolegal questions needs no further statement here. However, it is felt that there is need of statistical analysis of the mass of death records piled up by the coroner's service. In such analysis various broad relationships are involved since the coroner's work integrates with numerous other departments and agencies of the body politic. Some of these relationships will be briefly mentioned here as indicating the scope of the work.

From the Department of Pathology of Northwestern University Medical School.

1. Schultz, O. T., and Morgan, E. M.: The Coroner and the Medical Examiner, National Research Council Bulletin No. 64, Washington, D. C., 1928. Martland, H. S.: Proc. Inst. Med. Chicago **9**:261, 1933.

The primary growth of the coroner's function related to questions of criminal acts in individual deaths, and such investigations are still perhaps the most widely known of his activities. In this capacity the coroner's physician is required to furnish to the state's attorney all immediate material evidence of crime, as well as an opinion as to the determining cause of death and the associated pathologico-anatomic findings in the dead body. Present day trends of crime soon bring this activity into relation with gangism, robbery and criminal abortion, to mention some of the crime ramifications.

The coroner at present reviews and certifies all deaths which are not due to so-called natural causes, and so furnishes to the health department a rapidly growing mass of statistics on deaths related to external traumas. His investigation of circumstances leading to accidental deaths of workingmen gives information to the state industrial department valuable in formulating preventive safety measures and in determining compensable injuries. Public safety organizations likewise find in his work material support for measures and public education looking to the prevention of accidents. Insurance companies have a rich fund of information provided by the coroner on which to shape policies in regard to industrial injuries or transportation accidents, accidental poisonings and suicides, for example.

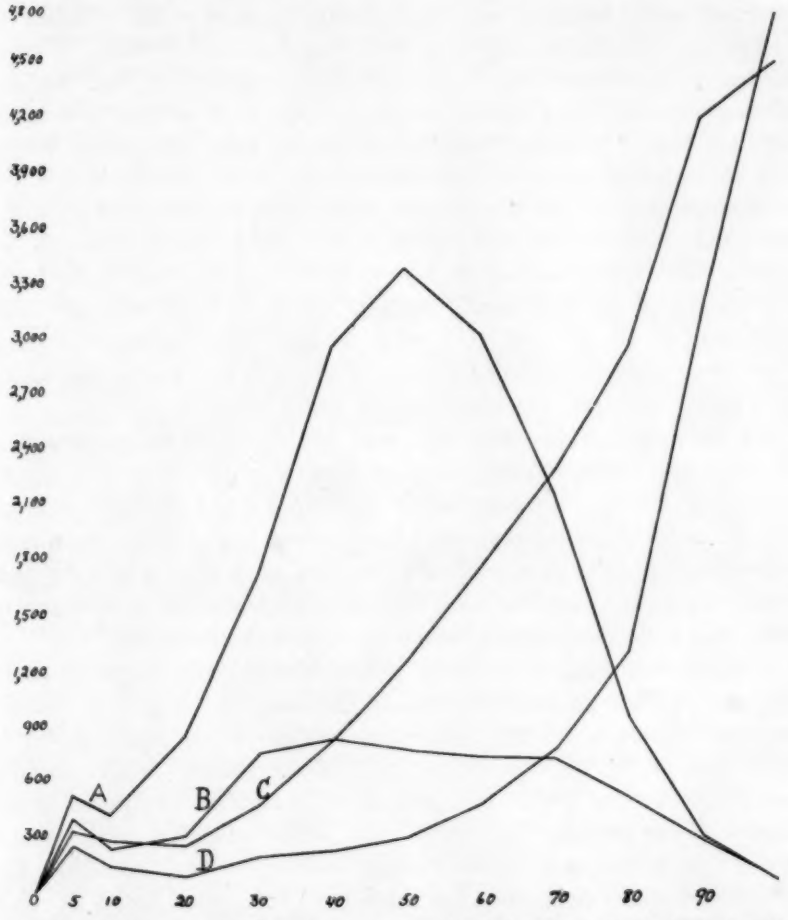
In addition, since various previously existent or intercurrent illnesses and physical disabilities may play a significant rôle in the outcome of injuries an analysis of mass data revealing the importance of these and their mode of action will be valuable to practicing physicians and to pathologists.

In all of the aforementioned relationships of the services performed by the coroner's physicians, it may be added, perhaps unnecessarily, that the value of the coroner's information depends on the type of pathologic investigation done.

GENERAL STATISTICAL SURVEY

The total number of deaths investigated by the coroner's physicians in the four year period, 22,206, represents 13 per cent of the total number of deaths in the area. A large proportion of them occurred within the city of Chicago, and of the city's total number of deaths they comprised 15.5 per cent. Previously the number of coroner's cases had been much higher, reaching 8,374 in 1926, for example, or 20 per cent of the total number of deaths in the county. The reduction in numbers was brought about by certain changes in the rules for acceptance of cases. Among these was the abatement of a rule requiring report to the coroner of any death occurring in a hospital within twenty-four hours after the patient's admittance. Another was the refusal to

view any case of death occurring at home if a physician had been summoned for the first time at about the time of death. If the physician would not sign the death certificate but supposed the death to be due to natural causes, the case was referred to the local registrar, under the department of health.



A and *B* show the total numbers respectively of males and females who died in the different age groups; *C* and *D*, the rates of death of males and females per hundred thousand of population. The age decades are indicated at the bottom.

Sex.—There was a total of 16,426 males and 5,425 females whose deaths were investigated, with 355 fetuses not included, making a proportion of males to females of about 3:1. The types of risks resulting in so-called coroner's deaths certainly are assumed much more frequently by males. Among these may be mentioned heavy mechanical

labor, other physical activity with exposure to injury, drunkenness, suicide and homicide.

Age.—Such risks among others are operative over the greater part of the life span, with a resultant increase of mortality. Beginning at the age of 10 the proportion of males to females in successive decades was roughly 3:1, 2:1, 3.5:1, 5:1, 4:1, 3:1 and 2:1. This difference was decreased at the extremes of life, as might be expected.

Deaths of children under 5 years of age numbered 925. A large number of these were due to some type of asphyxiation, such as that from smothering, from aspiration of a foreign body or from a respiratory infection. A large number were due to falls. In deaths due to falls or to accidents of transportation fracture of the skull was the common finding. Two factors are probably operative in this injury. One is the lack of protection afforded by a weak general musculature and the other is the ratio of the weight of the head to that of the body. The weight of the head is 27 per cent of that of the body at birth, decreasing to 16 per cent at 5 years of age, while in the adult it is 7 per cent. Another important cause of death in this group was burns, most frequently from hot water, coffee, tea or soup.

In the group of advanced age, with 554 deaths in those more than 80 years old, cardiovascular mishaps were responsible for the largest number of deaths. Cardiac failure on a myocardial or coronary basis was the most frequent cause, with spontaneous hemorrhage, thrombosis and embolism next. A second very frequent cause of death in the aged group was injury sustained in a fall, often accompanied by fracture of bones and quite commonly terminating in bronchopneumonia.

Fetuses numbered 355. These represented largely calls to the police who picked them up and took them to the morgue. It is very possible that this number is a wholly inadequate measure of the total number of dead fetuses. Those reported varied from very early fetuses to fully matured infants at term. Evidence of malformation or disease of the infants or membranes was quite rare. The suspicion must remain strong that an abortion carried through without medical attendance and with surreptitious disposal of the products of conception savors of criminal practice. The full-term infants gave mute evidence of all forms of taking of life and, often, attempted destruction of the body. Hemorrhage from the cut, untied cord, choking, smothering and blows on the head were the most frequent means used to kill.

Little comment is ever made on this taking of life, and it certainly offers problems difficult to solve. It is likely this difficulty which governs the lack of legal investigation into most of such cases, which are quite largely cases of either murder or manslaughter.

Race.—The chief racial elements found in the population are the Caucasian and the Negro. Of these the white persons made up 89 per cent and the black 11 per cent of the coroner's deaths. Only occasional deaths of persons of other races appeared. The yellow race had a list of 44 cases. The Negro population of the area is 250,000 in a total of 4,000,000, or about 6 per cent. It is seen that deaths in the Negro population appeared as coroner's cases in a somewhat higher ratio than deaths of the whites. As to location, practically all of the bodies of Negroes were found in colored districts or at the morgue.

Length of History.—The majority of cases showed, as expected, a short duration of time from the onset of trouble to death; in 17,401 there was a history of less than twenty-four hours. A large share of the deaths, then, were of emergency nature. Of cases with a history of from one to fourteen days there were 3,049. Of those with a history of from two to eight weeks there were 761, and of those with a history of from two to twelve months there were 427, while in 213 cases the

Total Number of Deaths by Months

	Nov.	Dec.	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.
1928	789	732	...	...	...	...	...	...	...	...	...	...
1929	381	409	574	390	564	566	434	396	366	373	334	386
1930	456	418	385	401	378	433	399	429	441	438	361	363
1931	508	510	414	368	402	421	435	480	525	519	480	513
1932	...	...	499	495	528	503	502	506	527	507	481	487
Total	2,134	2,069	1,872	1,654	1,872	1,923	1,770	1,811	1,859	1,837	1,656	1,749

victim lived one year or more. Many things militate against large numbers in the later brackets, chief of which is the fact that a disorder lasting any considerable length of time is usually entrusted to a physician's care and thus noninjury cases are weeded out. The cases with longer history were usually claimed to have some association with injury, although this association often became less definite with time.

Time of Year.—This question was reviewed to find if any seasonal influence might produce a marked variation of the number of cases. The total numbers by months as given in the table show no consistent influence exerted by the time of year. The large number of factors which produce coroner's deaths seem to equalize the total numbers of cases so that any seasonal difference is absorbed.

OPERATION OF CORONER SYSTEM

Places of Investigation.—Ordinarily only certain criminal cases or cases suspected of being criminal require the viewing of the body by a coroner's physician before it is moved. Quite frequently in such cases, also, when death is not instantaneous the victim is rushed by

police ambulance to a hospital. If the patient is dead on arrival or before admittance to the hospital, the body is taken to the nearest undertaker or to any other requested by a relative. Undertakers also receive bodies in cases of sudden death on the street or in public buildings. In addition, on permission from the coroner's office a large number of bodies are removed by undertakers from hospitals and homes before they are seen by the coroner's physician.

Undertakers' Morgues: The majority of cases, then, are investigated at undertakers' morgues. The difficulties inherent in this situation have been discussed by others.[2] Of the total of 22,206 cases for the period, 12,927, or 58.2 per cent, were examined in undertakers' morgues. Of these, 2,414 were given pathologic investigation, the number of autopsies constituting 39.4 per cent of the total number of autopsies. Autopsy was made in 18.7 per cent of cases investigated at undertakers' morgues.

Coroner's Morgue: The coroner's morgue receives bodies from the county hospital in coroner's cases in which the victims were admitted before death, and from the hospital at the city jail. Also unknown and unclaimed bodies from various other places are received. These cases are investigated entirely by one coroner's physician assigned to work in the morgue for a given period.

The total number of cases handled at the county morgue was 5,240. This represents nearly one fourth of the total number of coroner's cases. In 2,799 of these autopsies were made, or in 53.4 per cent. Also there were brought to the morgue 355 fetuses.

The advantages inherent in such a central workshop as the county morgue are numerous. Reliable information is obtained before death in most of the cases, and often from the living patient in the hospital. The relationship of previous diseases to the present trauma as the cause of death can be better evaluated with historical and clinical data available. As to the work itself the facilities of an organized morgue are offered.

This working arrangement is reflected in the number of complete investigations, accompanied by autopsies, performed at the morgue—2,799 on 5,240 bodies as compared with 3,329 on 16,966 outside bodies. The percentage of autopsies at the morgue thus reaches 53.4 as compared with 19.6 outside.

Conditions at the county morgue, however, furnish but few of the advantages which might arise from a central pathologic institute housing a general morgue to take care of all coroner's cases, with provision for pathologic or other medical scientific research under the direction of a permanent full-time pathologist. At present the work at the morgue is necessarily limited to a routine handling of individual cases as they are presented.

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2. Chandler, A. H.: Boston M. & S. J. **194**:728, 1926.

Hospitals: The remainder of the cases, numbering 3,684, or 16.6 per cent of the total, were taken care of mostly in scattered hospitals with a few at private homes. Among these cases there were 915 autopsies, the percentage being 24.8. This work is done under field conditions with many influences in action rendering investigation less satisfactory, from the standpoint of the coroner's physician, than in the morgue. While a larger proportion of this group than of that found at the county hospital is of the accident-with-sudden-death type, this larger proportion is not enough to account for the fact that the percentage of autopsies is less than half that at the county morgue.

Disposal of Cases.—Rejections: It is left somewhat to the discretion of the coroner's physician as to what disposal is made of the cases assigned to him. If he finds nothing in the circumstances to warrant proceeding further with a given case it may be rejected and no record of the case filed. With intelligent selection at the central office these cases are few.

External Examinations: The larger proportion of cases receive only "viewing," or external examination of the body and sometimes the surroundings, clothing or other externals to establish identity and perhaps evidences of external injury. Such external physical findings are considered together with the history in determining the cause of death. These cases numbered 16,078, or 72.4 per cent of the total.

Much objection may be raised against the policy involved in certifying causes of death without certainty as to the final pathologic condition. Any one who has been engaged in medical work on coroner's cases recognizes the type of apparently simple case of death from natural causes which is much complicated later by the uncovering of information which should have been proved by autopsy in the beginning. It is stated legally to be the duty of the coroner or his deputy to take charge of the body assigned to him by law and by his investigations to determine the cause of death. The intent of the law seems clearly shown, but its operation is vitiated by certain interpretations and restrictions, such as that limiting autopsy to cases of death from known or strongly supposed external causes.

Autopsies: A full autopsy would appear to be the only means of certifying the cause of death, certainly in most coroner's cases. One might exclude from this requirement cases which have had competent clinical investigation with a satisfactory determined pathologic cause of death. Even here, however, there may be interpretative errors clinically [3] with the best of conditions and experience. When this basic requirement for accuracy is sacrificed politically to various interested parties the medical certification of cause of death is stultified to that extent.

3. Cabot, R. C.: J. A. M. A. **59**:2295, 1912.

The cases in which autopsies were made, 6,128, comprised 27.9 per cent of the total number of cases. Of the autopsies, 4,389 were held in cases of death from external trauma, or in 26.4 per cent of such deaths, and 1,739 in cases of death from disease, or in 30.9 per cent of such deaths.

Certifications: Every case investigated must be either signed out by death certificate or referred to the central office for an inquest. The investigative function of the physician ends with determining the cause and as much as possible of the manner of death. If this seems to involve no legal liability, the coroner's physician is allowed to dispose of the case directly by signing a death certificate. In the period under consideration 5,628 cases, or about one fourth of the total number, were so handled.

Most of the cases with natural causes of death fall into this category, although if any suspicious circumstance exists or is declared concerning such a cause of death, inquest may be demanded.

Inquests: All other cases, 16,223, were completed by coroner's inquest. In such instances, the final determinative circumstances of death, if found, are passed on by a coroner's jury, whose verdict may close the case unless further legal action is indicated by some agency other than the coroner's office.

The latitude allowed the physician in choosing between the certificate and the inquest in the disposal of a case is determined by the policy of the coroner in office. It certainly would be much more economical as well as helpful in securing uniformity of policy if the type of case demanding the deliberations of a coroner's jury were more strictly defined.

INJURIES AS CAUSES OF DEATH

All causes of death in coroner's cases have been considered under the general headings of injury and sickness. When injury and sickness were intercurrent, the primary cause of death as indicated by the report of the coroner's physician has been followed.

The general rule is that any death preceded by an external injury shall be reported to the coroner's office. In application this includes any death following a recent injury of serious extent, and any death following an old injury if there is a supposed causal relationship. The trauma may arise in any manner or from any agency.

Accidents.—Accidental deaths naturally make up the larger share of the deaths that concern the coroner, and their number must increase with the complexity of a mechanized civilization. For convenience they are divided into three groups.

1. Industrial accidents resulting in death reported to the coroner numbered 610 for the four years. This remarkably low average of

153 deaths per annum reflects the modern evolution of safety devices and of "safety consciousness" in both employer and worker. The proportion of men to women killed was that of 100:1, which also indicates the average employment ratio of the sexes in hazardous occupations.

The coroner's usefulness in industrial cases depends on an immediate impartial review of the manner of the accident and a determination of the complete cause of death by the coroner's physician. The determined circumstances of death furnish data for safety recommendations, as well as information which may or may not support claims of dependents for compensation. Closer cooperation between the department of labor and the coroner's office than now exists seems therefore to be desirable in the study of the problems offered in industrial deaths.

Coroner's physicians at present may be employed by either party in a suit before the state compensation board as expert witnesses in the coroner's cases which have been assigned to them since, as county employees, they owe no special duty to the state compensation board. Further, the compensation board has no power of determining the cause of death in any case at issue other than by records or witnesses available. If industrial deaths were regarded as deaths in which autopsy is mandatory, complete data as to the cause of death could be had for record, thus wiping out frequently long argument and pure speculation.

2. Deaths from accidents of transportation numbered 10,768, or very nearly one half of all the coroner's deaths. The average of 2,692 deaths each year was 8 per cent of all deaths from whatever cause. This tremendous sacrifice of human life has been the subject of much writing and of some serious thinking. However, during the stage of development of rapid road transportation the toll of lives increased. It seems to have reached a peak and for some time has remained nearly stationary. The figures for the four consecutive years in question are 2,627, 2,794, 2,826 and 2,521. However, if the road development and present mechanical safety devices are again rendered inefficient by demands for increased speed the numbers of deaths may again increase.

The automobile gave by far the larger number of deaths, with 7,653 deaths directly charged to it and 745 more charged to it and to some other agency jointly. Railroads claimed 1,609 lives, but very few of passengers; quite a few of these lives were those of railway employees, but the greater proportion were exacted of persons not included in either of these groups. Street cars killed directly 393. Various other means of transportation added a few more deaths to the list.

3. In the group of deaths from miscellaneous accidents only those causes are considered here which piled up considerable numbers of fatalities.

Burns were responsible for 640 deaths, of which 409 occurred in adults and 231 in children. As noted before of children's deaths, those of infants were caused mostly by their being burned by hot liquids, and those of children 5 years of age or older, mostly by fire igniting their clothing. Fatal burns of adults were generally by fire. Several deaths occurred from igniting the bedclothes with cigarets but usually in persons who were known to be or who probably were addicted to overconsumption of alcohol. The history of alcoholism was so general that it would appear to be a definite hazard for a drunken cigaret habitué to be put to bed with cigarets and matches within reach.

Of asphyxial deaths (aside from suicides), numbering 470, a large share was caused by illuminating gas at home. A portion of the public does not yet realize the possible danger of a gas-burner attached by a temporary, often leaky connection such as a rubber hose, or the danger of a gas-heater, especially a stove, in a small unventilated room. Quite a few deaths from gas occurred as a result of going to sleep in a closed room with water or other liquid heating over a gas flame. When the liquid boiled over the fire was extinguished but the gas continued to escape.

Illuminating gas is a highly complex mixture the properties of which are imperfectly understood by the average consumer. This ignorance should be assumed to be in effect by the supply companies and a warning as to the common dangerous errors in the use of gas posted in every gas user's home. The supply companies should be required to post such warnings.

It is probable that many suicides by gas are called accidental because of lack of proof or other reasons. This is especially true of suicides by motor exhaust gas, which ran second among causes of deaths from accidental asphyxia.

Deaths from drowning, aside from suicides, are divided into two groups: those determined to be accidental, 368, and those in which the circumstances remained undetermined, 345, or a total of 713.

It is significant, from a legal standpoint, that in nearly half of the cases of drowning the circumstances remained undetermined. It is true that they offer some of the most puzzling of medicolegal problems. Many drowned persons are picked up floating after an indefinite time in the water, often in an advanced state of decomposition and commonly devoid of ordinary identification marks. Ruling out foul play may be difficult [4] and decision as to accident or suicide impossible. A very accurate chemical method has been devised [5] to determine whether death occurred by drowning or not. In this regard, the question of

4. Buetz, G.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:557, 1932.
5. Gettler, A. O.: J. A. M. A. **77**:1650, 1921.

mode of death in drowning arises again. This was investigated recently in animals,[6] with the finding that considerable amounts of water entered the lungs. In human beings, with different types of reflexes, however, death in drowning may not always result from the entry of water into the lungs.

Accidental falls causing death occurred in almost every conceivable manner, some of them being rather trivial in nature. The most of them were included in falls on the floor, 178 cases, and falls from high places, 433 cases.

The falls on the floor included all simple falls from the standing or sitting posture to the level of the feet. Death was caused from fractured skull or ruptured viscus, or late from pulmonary embolism or bronchopneumonia or other infections. The last named condition resulted in death in old people, for whom especially falls have much danger. Generally death from a minor fall presupposed some added hazardous factor such as age, weakness, sickness, drunkenness or striking against some projecting solid body.

The falls from high places again bring up the question of possible suicide in many instances. This group probably is larger than it should be, since all unproved cases, even though the question as to possible suicide may have been present, were classed as accidental.

Falls from hospital windows were responsible for 14 deaths. While this included the inevitable number of disoriented persons who eluded all restrictions, yet there was a marked proportion of patients with incurable maladies, such as malignant tumor, who chose this way out of their difficulties. Since the hospital assumes a certain responsibility for its patients, and since there is no way of knowing which patient may be seized by an impulse to hurl himself out of the window, it would seem much safer to provide some protective device at the windows. Yet the new hospitals which are built consistently ignore this feature of safety for the patients and freedom from legal attack for themselves.

Rupture of a single viscus from external trauma, aside from that caused by a penetrating wound, was found as the cause in 116 deaths. Most of these occurred from violent force such as results from falls or from the impact of a car or other heavy object, and so were generally associated with more or less shock. Several instances were found, however, of rupture of the liver or of the spleen in otherwise relatively minor accidents. Such a complication may be discovered easily if the patient is under supervision in a hospital, but most of these who died from this cause did not have such favorable care.

There were 6 instances of rupture of the small intestine, and in 2 of these the intestine was completely severed. A case which I observed may

6. Karpovich, P. V.: Arch. Path. **15**:828, 1933.

be cited as an example. A young man, struck in the back by an automobile and knocked down, walked several city blocks to his home, complaining only of pain in the back. Twelve hours later he suffered from abdominal pain, which was treated by a heavy dose of magnesium sulphate. This was repeated and the man died at home on the third day with no further care. Autopsy revealed generalized peritonitis. The ileum was completely severed at its midportion, as sharply as if cut by a knife. No trauma was found on dissecting the muscles of the back.

Suicides.—The tendency toward suicide is one of serious social concern in the present phase of evolution. The number of lives lost is considerable, but this is outweighed by the social-economic significance of the suicidal act itself. Each misfit or failure who sentences himself to death is thus voicing judgment against intolerable living conditions. So one might expect any sudden marked increase in the general stress of living to take its toll of those unable to adjust themselves to its demands. The association of suicides with economic crises is the most frequently cited illustration of this phenomenon. Suicides for this four year period numbered 2,723, which represents an average rate of 17 per hundred thousand. In the four years the rates ran successively 15.8, 17.3, 18.3 and 16.7.

On analysis of the cases of suicide there are found 2,138 males and 585 females, a proportion of almost 4:1, somewhat higher than most of the rates given.[7a] The white race accounted for almost all of the suicides, 2,607 cases; only 102 cases were contributed by the colored race. The remaining 14 cases occurred in various other races. This disproportionately high number of suicides of whites is in line with other published reports.[7b] The colored race seems to react very little to the depressing influences that promote suicidal attempts. As to the social condition of those who committed suicide, 1,542 were married, giving a suicide rate of 21.7; 608 were single, giving a rate of 15.9, and the remaining 573 were widowed or divorced, the rate reaching the high figure of 54.2. A recent report from New York City [8] likewise indicates rates for the latter class of persons much higher than those for single and married persons.

Of the methods used for committing suicide, shooting accounted for 802, considerably more than can be ascribed to any other means of self-destruction. Poisoning with 496 cases, hanging and strangulation with 494 and asphyxiation with 461 each accounted for about the same number. At a considerably lower level of numbers were those

7. Hoffman, F. L.: Suicide Problems, Newark, N. J., Prudential Insurance Company of America, 1927, (*a*) p. 249, (*b*) p. 15.

8. Hoffman, F. L.: Spectator, June 8, 1933.

who ended their lives by jumping from high places, 168, by cutting or stabbing themselves, 158, and by drowning, 116.

It is to be noted that the ratios of deaths by these various means are considerably different from those reported in late years from New York City.[9] In these reports illuminating gas has come to the fore as a ready means of self-destruction. In the report for 1931, cases in which gas was used numbered more than double those of any other form of suicide. Jumping from high places accounted for the second highest number, with hanging, shooting and poisoning following in the order given.

It is probable that a good proportion of those who attempt suicide use any means ready at hand for accomplishing the purpose. In Chicago the acquiring of firearms is easy and possessing them is not threatened with any serious consequences, so that they may be found rather commonly in homes. Whether a law such as the Sullivan law of New York would lessen the total number of suicides or would only divert those achieved by shooting into some other category remains questionable.

Jumping from high places has not increased so rapidly in this city as in New York City. It is given undue stress in the daily press because of its spectacular nature and because it has claimed some rather prominent victims. Possibly press emphasis may increase the numbers in the future.

Asphyxiation by gas, which is far ahead in numbers in New York, takes only fourth place in Cook County. I have found illuminating gas to be one of the commonest means of suicide in the cheap lodging houses of impoverished districts. Motor exhaust gas, which enjoyed a brief season of popularity, now accounts for rather few cases.

Abortions.—Figures on abortions are notoriously uncertain as to accuracy. In areas of strict registration most deaths from abortion are correctly reported, since reliable physicians are called before death or otherwise because of the danger of making an inaccurate report. Still the desire for secrecy is strong in many patients, and attempts to cover such deaths are not uncommon, even when the probability of criminal interference is not strong. It is obviously impossible to correlate deaths from abortions with the total number of abortions, because the latter must always remain an unknown quantity. The total number of deaths from abortions numbered 232, of which 40 were classed as due to criminal abortions. The low figure given for the latter class indicates the difficulty of proving criminal interruption of pregnancy, and the term "suspected criminal abortion" or "probable criminal abortion" cannot be used officially.

9. Norris, Charles: Statistical Report of the Chief Medical Examiner of the City of New York, New York.

Alcohol.—Alcohol was listed as a primary cause of death in 303 cases, other than those due to delirium tremens, and as a directly associated factor in 336 cases. These 639 cases represent very largely acute intoxications, with evidence of alcoholism outstanding. Some of the cases in the second group occurred in persons who were addicted to the use of alcoholic stimulants and who acquired pneumonia or cardiac decompensation or renal disease following alcoholic sprees. Numerous accidents entailing death were associated with acute alcoholism. No coroner's physician would subscribe to the old saying that God has the drunkard especially under his watchful care.

Alcohol as a remote or associated cause of death cannot at present be properly evaluated. It is commonly stated that those who are chronically subject to alcohol have a marked liability to acute infections of the lungs and to shock from external trauma, including surgical operations. Yet such association is usually not mentioned in death certificates. This discrepancy between general statement and specific citation renders it easy for workers on either side of the question of the deleterious effects of alcohol to get medical support for their crusades.

In the work of coroner's physicians the number of cases included as cases of alcoholism must vary considerably if this diagnosis is accepted from history and anatomic findings alone, or if it must be supported by chemical examination of specimens removed at autopsy. In this respect it is of interest that chemically proved cases of alcoholism in the four years numbered 278.

Only 3 cases of pellagra were reported, and but 1 of these was definitely diagnosed as postalcoholic. Skin lesions are common among the human wrecks who are listed for coroner's investigation. Various forms of dermatitis, fungous infections and insect bites often combine to give mixed pictures which may confuse specific diagnosis. Often skin lesions are accepted as such a usual finding in cases from lower social strata that no attempt is made to find in them evidences of the cause of death. It seems probable that postalcoholic pellagra is similar to the usual form,[10] and since statistics indicate its increasing incidence, persons who are known to have been or may have been chronically alcoholic should be carefully scrutinized from the standpoint of pellagra.

Homicides.—Homicide was accountable for 1,984 deaths in this period. Much has been written about killing in the United States as one of its major evidences of crime. The homicide rate has been given as the highest in the world. Much of this killing goes unpunished. Indeed, capital punishment was evoked most sparingly in this period of four years. The disturbing feature is that a high percentage of

10. Boggs, T. R., and Padget, P.: Bull. Johns Hopkins Hosp. **50**:21, 1932.

such crimes are directed or inspired by organized outlaws of society who are able to scoff at threatened reprisals.

The coroner's physician is able in cases of criminal homicide to furnish much valuable evidence to the state. An autopsy certifies the exact cause of death and gives irrefutable proof of the means used in producing death, such, for example, as bullets recovered, specimens removed for chemical examination in poisoning, in asphyxiation or in drowning, and proof of the means of strangulation, stabbing or striking with heavy objects.

The killed persons numbered 1,699 males and only 282 females, which is in line with the sex distribution usually reported.

The colored race had 679 homicides with a rate of 68 per hundred thousand, as compared with 1,284 among the whites and a rate of 8.6. This is the reverse of the racial tendency toward suicides. The homicidal mania of the colored race is responsible for very high rates of homicide in certain cities of the South which have a high percentage of colored population.

Shooting accounted for 2,435 cases. These were divided into 1,424 homicides, 802 suicides, which have already been discussed, 158 accidents and 53 undetermined.

The fact that shooting disposed of 72 per cent of the victims in all homicides is ready evidence of a widespread ownership of firearms, as well as of deplorable sociopolitical developments, which encourage crinimal use of these weapons.

Of other forms of homicide listed, cutting or stabbing accounted for 301 cases and blows on the head or body for 129. Scattered cases, only, were listed under various other methods of killing.

Traumatic Septicemia.—Coroner's cases in which septicemia caused death numbered only 103, or 26 per year. When it is remembered that this includes all cases arising from or associated with reported external trauma of whatever cause, some appreciation can be had of the remarkable advance in present day treatment of external trauma.

Tetanus.—Tetanus was recorded in 86 cases, or 21.5 per year. Though the number is low, these cases must be considered as sacrifices to public ignorance. By proper educational propaganda tetanus after Fourth of July celebrations has been made a rarity. The value of prophylactic treatment against tetanus after certain types of injuries generally could just as easily be made a matter of common knowledge.

Excessive Heat.—Heat was the cause of death in 176 coroner's cases. An attempt was made to subdivide the cases into those due to heat stroke and those due to heat exhaustion [11] but it was found impossible

11. Shattuck, G. C., and Hilferty, Margaret M.: Am. J. Trop. Med. **12**:223, 1932.

to do this from the data and diagnoses given. So the inclusive term "excessive heat" was used as recommended for the official list of causes of death. The total number of deaths certified as due to heat numbered 596, so that the coroner's cases made up 29.5 per cent of the total. The general tendency during extremes of weather is to assign the extremes of temperature as causes of many deaths which should properly be classed otherwise. It is felt that the coroner's reports represent well selected cases from the standpoint of diagnosis.

The larger number of cases occurred in persons past the age of 50. This, too, in spite of the fact that industrial and other exposure to heat must have been much greater in the more active younger persons. Practically no deaths from heat occurred in children. Persons at the extremes of life have an imperfect heat-regulating mechanism, but infants are rarely killed by heat because they are shielded from it. If the aged could be shielded just as carefully from overactivity or overexposure during hot weather there would undoubtedly be fewer tragedies due to heat among them.

Epilepsy.—Epilepsy, either of essential or jacksonian type, is often confused in the final state with recent injury to the head, delirium tremens and toxic psychosis. Coroner's cases are often woefully lacking in history, and clinical observations may have been only terminal or entirely lacking, so that factual material for reconstruction of a case that has reached the stage of death may be scanty. The lay witness, and occasionally the medical witness, is inclined to term almost any sort of convulsion "epileptic" and any delirium of sudden onset in a man "delirium tremens." Again the autopsy becomes the only method of investigation that gives facts.

Epilepsy was the cause of death in 52 cases. Some of the epileptic persons died in status epilepticus. Others perished in accidents resulting from epileptic attacks, such as falls or motor accidents with the epileptic person at the wheel. In the present mechanical age it may be difficult for an epileptic person attempting to lead an ordinary existence to avoid mechanical responsibilities, but certainly such risks to himself and others should be minimized.

Delirium Tremens.—Victims of this disorder came to their deaths almost always with intercurrent disease. Frequently the delirium was precipitated by an acute disease. Often also an attack was precipitated in a person chronically alcoholic by external trauma. What part was played by the intercurrent sickness or injury in causing death may be difficult to decide, so that, unless overbalanced by a definite history of inebriety, traumatic or toxic psychosis must be kept to the front until fully ruled out by autopsy.

DISEASES AS CAUSES OF DEATH

Sickness alone, or the so-called natural cause, is operative in many deaths that call for viewing by the coroner's physician. Especially is this true in sudden, perhaps unexplained deaths and deaths in which sickness is intercurrent with an external injury. In regard to the former group the coroner's physician is held responsible for certifying the cause of death as a matter of public policy, so that any possibly suspicious death may be properly investigated. In regard to the latter group many medicolegal questions arise as to criminal or civil responsibility.

In either group the autopsy is of prime importance. In sudden deaths arising largely on a basis of cardiovascular disease much pathologic investigation is still needed for better understanding of the processes involved. Most such pathologic material is lost to human benefit by being signed out on simple inquiry. When sickness complicates the course of trauma from external cause proper evaluation of the factors resulting in death can be made only by autopsy. All else is only approximation.

The total number of deaths from sickness was 5,618, or roughly one fourth of all the coroner's cases. In 1,739 of these, or a percentage of 30.9, autopsy was made.

Cardiovascular Disease.—Deaths from cardiovascular causes—heart disease including disease of the coronary artery, spontaneous hemorrhage of the brain and aneurysm—all combined numbered 3,586, or 63.8 per cent of all deaths from sickness.

The largest quota in this group was made up of the deaths from primary heart disease, which includes all forms leading to acute cardiac failure generally. There were 2,935 of these cases. There was also a complementary group of 240 cases in which death was due to disease of the coronary arteries.

A large proportion of the cases signed out as due to acute cardiac failure were "view" cases only. The rather typical history is that of a man of over 50 years with no history of current disease who collapsed while at some form of activity and died suddenly. Acute cardiac failure was given as the cause of death on the basis of probability, with the underlying pathologic condition not further proved.

Undoubtedly a much larger figure should be given for deaths from disease of the coronary arteries. The circumstances which render death reportable to the coroner quite naturally obtain in a considerable number of such cases. So the figure of 240 such deaths out of 3,175 deaths from acute cardiac failure of all forms indicates a probable insufficiency of examination into final causes.

Varied pathologic pictures were presented by the few autopsy reports in this group of sudden deaths. Besides cases of frank coronary throm-

bosis, there were many cases of chronic myocardial change mostly presumably on a vascular basis, unless associated with changes of the endocardium or pericardium suggesting other etiology. Ruptures of the wall of the heart were usually with recent coronary myomalacia, although rupture through a massive old scar of the left ventricle was seen. Massive hematopericardium appears to have resulted more often from rupture at the beginning of the aorta than from any other cause, this not necessarily as a consequence of syphilitic aortitis but sometimes as a result of formation of calcium plaques in the intima with development of dissecting aneurysm. A few cases of unsuspected acute endocarditis with fatal embolism and at least 1 case of acute annular ulcerative aortitis were found. There were several cases of ruptured unsuspected aneurysms in various locations. Massive cerebral hemorrhage accounted for several deaths, and likewise embolism after minor trauma, affecting the lungs or rarely the brain or the heart through a patent foramen ovale.

Spontaneous intracranial hemorrhage was diagnosed in 362 cases. Such a diagnosis in a case of immediate death without subsequent autopsy is much less in favor than formerly, since it is realized that intracranial hemorrhage does not as a rule kill instantly.

Nephritis.—Nephritis was assigned as the cause of death in 296 cases. The inclusion of these cases as coroner's cases was largely because of the tendency for coma to develop in persons with chronic nephritis on external trauma, exposure or toxemia. Acute glomerulonephritis, especially that superimposed on chronic nephritis, likewise developed with similar causes. Add to such etiology the fact that a considerable number of homeless persons have this disease and are without previous medical care, and that when they are found in late coma there is not sufficient time before death to rule out other possible causes besides nephritis. An autopsy certainly is demanded in all coroner's cases in which a person dies in coma and the clinical studies are not conclusive.

Pneumonia.—Pneumonia was written into the records of 1,608 cases, a number running surprisingly close to half that of the entire cardiovascular group.

There were 693 cases of primary pneumonia. The number of these was swelled by cases occurring in infants, many of whom died after a few days of what was considered a "cold," without medical attendance. Some aged persons also showed little reaction to such a serious infection and died suddenly at home with pneumonia unsuspected until autopsy. Persons with chronic alcoholism, especially those of lower economic strata, who slept off a bout with liquor exposed to inclement elements swelled the list of those who succumbed to pneumonia. Often derelicts, with no living place, they were sometimes found dead in out-of-the-way places, with pneumonia as the immediate cause of death.

Much harder to explain were the occasional cases of lobar pneumonia in adults with death following shortly after a dramatic onset of symptoms. An illustrative case may be cited. An apparently vigorous white woman of 40 years with no known complaint went into the city to transact business. While walking about she suddenly fell unconscious, was taken to a hospital and died four hours later without regaining consciousness. Complete autopsy disclosed only lobar pneumonia with an early gray stage of consolidation of the right lower and middle lobes. Such cases stress the possibility of pneumonia without the usual marked symptoms, which may go undiagnosed to either recovery or death.

A second group of cases of pneumonia is made up of those in which the condition was associated with external trauma, numbering 915. Here again persons at the extremes of life and persons who were debilitated comprise by far the largest portion. This was so striking in going over the cases that on reading "Patient, 65 years +, fall, with injury of several days' duration, and death" a finding of pneumonia could be reasonably predicted.

However, a considerable number of these cases were found in young persons and adults of middle life who had suffered trauma of varying severity. I believe, though without final proof, that in these pneumonia may arise on etiologic grounds quite different from those on which pneumonia arises in the less sturdy group. In the aged and debilitated persons the blame is generally laid on an inefficient circulation with congestion of the lungs, which prepares the ground for infection. It seems possible that in younger persons pulmonary infections may arise in areas in which circulation has been impaired by small emboli. The lungs as an efficient strainer for the venous blood undoubtedly intercept many foreign masses in the blood stream without symptoms of damage of the lungs arising. A shower of such small emboli might seriously impair the circulation of areas of the lung, without completely shutting it off, in a person with an efficient general circulatory function.

Still other factors were brought into play in late cases of exposure to gas, either illuminating or automobile exhaust gas, and in late cases of poisoning by depressant drugs such as opium, chloral, acetanilid, bromides and others. Many of the victims seemed to recover entirely from the original injuries, but within a few days contracted pneumonia, generally of lobular type, from which they died. In these cases depression of the respiratory function must be given a prominent rôle among etiologic factors, although some direct injury to the lungs is not ruled out.

Unfortunately, as to the whole question of pneumonia in cases of injury, this survey can cover only the fatal cases of injury, among

16,588 of which there were 915 which terminated in pneumonia. However, enough is shown of the seriousness of pulmonary complications to emphasize the need of clinical measures of prophylaxis. It is not too much to expect that the lag in the practical application of newer discoveries might be overcome to the extent of using as a routine the principle of hyperventilation of the lungs [12] in at least those cases of trauma severe enough to induce inactivity. Hyperventilation might be made a still more valuable procedure by using it periodically for some time after the injury.

Status Thymicolymphaticus.—This euphonious term was used rather sparingly in certificates of death. Only 41 cases were ascribed to this cause. The present reaction against such a diagnosis is well presented in the report of the British Commission.[13] But as long as the diagnosis is accepted the term will be found decorating death certificates. Its chief usefulness in the coroner's cases of sudden death and in those of obscure cause coming under the view of any lazy-minded practitioner of medicine arises from its eminent respectability and all-inclusive scope.

Tuberculosis.—Tuberculosis appears to be generally outside the scope of the coroner's inquiry, yet 233 cases were listed in which it was given as the primary cause of death. Certain points are brought out by these cases. First, that among the admittedly large number of people with active tuberculosis mingling in the general activities of life, accidents may occur. The shock of external trauma and the stress of the subsequent confinement show a likeliness to hasten the progress of existing active tuberculous lesions or indeed to light up new ones from latent foci. Next, an appreciable number of tuberculous people, perhaps euphoric, perhaps really carrying on fairly well, go to the end of their lives without medical care. The frequency of uncared-for cases among drug-users and prostitutes is too well known to need special comment here.

Diabetes.—The 54 cases in which this condition was found to be the cause of death came into the coroner's group principally for two reasons. One is that persons suffering from diabetes readily contract serious infections, perhaps ending in septicemia, from external trauma. The other is that many persons in whom diabetes is previously unrecognized or untreated die in diabetic coma.

Pancreatitis.—Acute hemorrhagic pancreatitis occurred in 5 cases. The frequently dramatic onset and short course of this disease may lead the laity to suspect it of resulting from external trauma. Especially is this true if the victim has recently undergone some special physical

12. Henderson, Y.; Haggard, W., and Coburn, R. C.: J. A. M. A. **74**:783, 1920.

13. Young, M., and Turnbull, H. M.: J. Path. & Bact. **34**:213, 1931.

stress or injury. While cases have been reported[14] in which such association occurred, certainly medicolegally opinion should be reserved pending the careful ruling out of other more frequent causes.

Peptic Ulcer.—In 28 cases peptic ulcer caused death, by hemorrhage or perforation. Death by hemorrhage from a previously "silent" ulcer was noted. Again the vexing question arose as to the possibility of external trauma causing such a complication of ulcer of the stomach. Uncertainty was often added to by the passage of a considerable period of time between the supposed injury and the evidence of the complication.

Hepatic Disease.—Thirty-five deaths investigated by the coroner's physicians were due to diseases of the liver. Acute yellow atrophy was accountable for about two thirds of the cases. However, in the same length of time there were 94 fatal cases of acute yellow atrophy in the county. An increase of this disease has been feared from the extensive use of arsenical and coal tar medicines. Such cases, if recognized and properly reported, come under the coroner's investigation. Since the coroner's cases have been few as compared with the total number it appears that the feared increase has not occurred or that the reporting has been inaccurate.

Acute Infections.—Cases of acute infectious disease turned over to the coroner's service for investigation numbered 27. While such cases generally seem more properly to belong to the department of health, sudden death in a case in which the condition was undiagnosed, such as an asphyxial death with diphtheria, might call for an exercise of the coroner's power of complete investigation.

Syphilis.—This disease as a cause of death was recorded in 18 cases. I do not believe that this figure represents the total number of cases in which syphilis is a factor in causing death. In view of the type of cases included among the coroner's cases syphilis as a cause of death should rank more prominently. As long, however, as syphilis is a cause of death that carries not only a social but often also a financial penalty in the possible loss of life insurance or industrial insurance, the urge to concealment will operate. Besides allowing reasonable doubts to aid in salving the pride or economics of the family of the deceased, an examiner hesitates to expose himself to a possible suit for damages by including *de novo* the term "syphilis" in a death certificate, unless the diagnosis can be defended beyond peradventure.

Tumors.—Malignant tumors caused death in 157 cases. Most of these cases were those of persons in whom malignant growths had been diagnosed before death or in whom malignant growths had been sus-

14. Stuart, M. C.: Northwest Med. **20**:58, 1921.

pected but who had gone without medical attendance. Some exceptions were cases of persons who died in coma with primary or metastatic tumor of the brain, sometimes with superimposed acute hemorrhage, and of persons with minor injuries who had pathologic bone fractures with tumor, or of those whose tumors arose following external trauma.

As regards the first group of persons many were members of so-called religous cults which find their most fallow and remunerative fields among the victims of chronic diseases but at the end require a special public service to sign the death certificates.

The question of a single external trauma as the direct cause of malignant tumor remains yet to be proved, although there have been numerous coincidental possibilities observed among sarcomas. Carcinoma has not indicated such immediate relationship, except rarely.[15] Some of the cases in this group are those in which an effort was made to link the death etiologically with a reported external injury.

Hemorrhage.—Massive hemorrhage not induced by external trauma was found in 101 cases, aside from intracranial hemorrhage. Since the hemorrhage in itself was not the primary disease these cases were considered with those of the disease causing the bleeding. Hemorrhages from aneurysms, peptic ulcers and tuberculous lungs made up the majority, with hemorrhages from ruptured varices, especially of the esophagus, shown in a few cases. No case was listed in which a hemorrhagic diathesis was the cause of death.

A type of hemorrhage totally unrelated to the types mentioned is the late secondary hemorrhage occurring after external trauma. Only 3 such cases were given, so the interest of this type lies largely in its rarity. Since this type occurs with wound infection, the low number seems again to emphasize the present day advance in caring for wounds.

Pulmonary Embolism.—Massive pulmonary embolism after injury other than surgical operation terminated life in 57 cases. Embolism occurred with all grades of severity of injury and apparently with all degrees of motility of the subject. It was found in severely injured, bedfast patients and in slightly injured persons at full activity. It is not felt that any conclusion is permitted from such data, however, since the total number of nonfatal injuries with subsequent activity or inactivity cannot be determined, even though other variables could be evaluated.

OTHER CAUSES OF DEATH

Numerous other medical causes of death are represented by a few cases each. They were generally called into question by some suspicious circumstance about the death itself or because of lack of medical atten-

15. Wells, H. G., and Cannon, P. R.: Tr. Chicago Path. Soc. **13**:183, 1930.

dance. Because of the scattering of these causes no special mention will be made of them.

SUMMARY

A review is presented of the 22,206 deaths investigated by the coroner's staff of Cook County, Ill., from November, 1928, to November, 1932. This number is 13 per cent of the total number of deaths in the area. These deaths occurred in 16,426 males and 5,425 females. The colored race, making up about 6 per cent of the population, contributed 11 per cent of the deaths. With the deaths grouped as to age, the percentage death rate is found to have been highest toward the extremes of life. In actual numbers, more deaths were found in males from 40 to 50 years of age, while in females the curve rose to an almost level plateau extending from 20 to 70 years of age. There were 355 fetuses; the causes of death remained mostly unknown. Different seasons of the year were not found to influence appreciably the total number of cases.

There were 12,927 cases examined in undertakers' morgues with an autopsy percentage of 18.7, 5,240 at the Cook County morgue, in 53.4 per cent of which autopsies were made, and 3,684 at various hospitals, in 24.8 per cent of which autopsies were made. The percentage of autopsies in all cases in all places of examination was 27.6. Death certificates were signed by coroner's physicians in 5,628 cases, while in the remainder, 16,223 cases, the report of death was completed by inquest.

Deaths from external traumas numbered 16,588. The following types of cases of injury resulting in death are considered: accidents of transportation, 10,768; suicides, 2,723; homicides, 1,984; burns, 640; falls, 611; industrial accidents, 610; asphyxiations, 470; alcoholic injury as a primary factor, 303, and as an associated factor, 336; abortions, 232; excessive heat, 176.

The duration of life following injury was short in most cases, with 17,401 of the cases terminating in death in less than twenty-four hours. In the remaining cases, 4,450, not including those of fetuses, the histories varied in length up to one year or more.

Cases in which sickness was the only or the associated cause of death numbered 5,618. Specific diagnoses were given as follows: Among cardiovascular diseases, primary heart disease, 2,935, with a complementary group of coronary arterial disease, 240, and spontaneous intracranial hemorrhage, 362; pneumonia as the primary cause of death, 693, and associated with injury or other cause, 915; nephritis, 296; tuberculosis, 233; malignant tumor, 157; massive hemorrhage not associated with external trauma, 101; massive pulmonary embolism

after disease or injury other than surgical, 57; diabetes, 54; status thymicolymphaticus, 41. Numerous other diagnoses were given with few deaths.

This review is presented as an attempt to stress the general importance of the great mass of coroner's deaths both as to sociopolitical and economic significance and as to the valuable medical lessons to be derived from the course of injuries or diseases, either as separate entities or when intercurrent.

General Review

ENDOMETRIAL HYPERPLASIA

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Endometrial hyperplasia is an important gynecological condition characterized by profuse and irregular hemorrhages, hyperplastic endometrium and absence of functioning corpora lutea. It is an important disorder of the menstrual function, and before considering it in detail it seems wise to review a few important facts concerning the normal physiology of menstruation. Recent work has advanced knowledge of this process considerably and given some insight into it.

THE MENSTRUAL MECHANISM

The normal, healthy woman menstruates at more or less regular intervals of about twenty-eight days. Following menstruation the endometrium undergoes a gradual proliferation up to the time of ovulation, which occurs at about the ninth postmenstrual day. Then the epithelium ceases to proliferate and begins to undergo secretory changes. When menstruation begins, the endometrium rapidly disintegrates and is cast off. Following menstruation the epithelium grows out from the glands and covers the desquamated area, and the proliferation starts again. These cyclic changes in the endometrium are dependent on cyclic changes occurring in the ovary. In the latter organ there is a period of follicular ripening following menstruation. On or near the ninth postmenstrual day this process terminates in the rupture of the follicle and the discharge of the ovum. Following follicular rupture, or ovulation, the lining cells of the ruptured follicle begin to grow and form the corpus luteum. During the process of follicular ripening the follicles secrete a hormone which stimulates the growth of the endometrium. Principles having an estrogenic action or extracts containing such principles have been variously designated (female sex hormone, theelin, amniotin, progy-

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non, estrin, etc.). Since the hormone has the capacity to produce estrus in the spayed animal, the term estrogenic substance has seemed particularly appropriate. In the ovary that substance is found in the graafian follicle, interstitial tissue and corpus luteum. However, the follicles are generally considered as the main source of this secretion. Substances of a similar nature are found in the blood of the menstrual discharge, in the placenta, and in the blood and urine during pregnancy. A chemically pure substance having, so far as is known, the same physiologic effects has been isolated by Doisy, Veler and Thayer [1] and by Butenandt [2] from the urine of pregnant women. Following ovulation, the follicle undergoes a series of changes which result in the formation of the corpus luteum. Fraenkel [3] first definitely proved that this structure had the properties of an endocrine gland. Recently Corner and Allen [4] isolated a hormone from the corpus luteum. This hormone has no effect on the endometrium of the castrated animal unless the endometrium has previously been sensitized with the estrogenic hormone. If so, the proliferative changes produced in the endometrium as a result of that hormone are modified by the action of the corpus luteum hormone, and premenstrual or progestational changes occur. These two hormones provide the stimulus for the endometrial changes taking place in the interval between the end of one period and the beginning of the next. Those before ovulation are caused by the estrogenic substance and those following ovulation by the combined effects of the estrogenic and the corpus luteum hormone.

The premenstrual phase is terminated by the onset of menstruation. The actual cause of the menstrual bleeding is considered by Hartman, Firor and Geiling [5] to be a special menstrual hormone which originates in the anterior pituitary gland. On the other hand, Saiki [6] failed to confirm their findings and produced good evidence that menstruation is a degenerative process resulting from a decline in the ovarian hormones. According to this view, the endometrium is dependent on the hormones for its growth stimulus. When the growth stimulus is removed, growth stops and the tissue regresses to its former condition. In the human endometrium and in that of the monkey this regression is associated with certain vascular phenomena which result in menstruation. It has been known for some time that removal of the human ovaries in

1. Doisy, E. A.; Veler, C. D., and Thayer, S.: J. Biol. Chem. **86**:499, 1930.
2. Butenandt, A.: Deutsche med. Wchnschr. **55**:2171, 1929.
3. Fraenkel, L.: Arch. f. Gynäk. **91**:705, 1910.
4. Corner, G. W., and Allen, W. M.: Am. J. Physiol. **88**:326, 1929. Allen, W. M.: Am. J. Physiol. **92**:174, 1930.
5. Hartman, C. G.; Firor, W. M., and Geiling, E. M. K.: Am. J. Physiol. **95**:662, 1930.
6. Saiki, S.: Am. J. Physiol. **100**:8, 1932.

the premenstrual phase results in the premature appearance of the menstrual flow. This clinical fact lends support to the views of Saiki, as does the earlier work of Allen [7] who noted menstruation in monkeys following injections of theelin. Recently Werner and Collier [8] observed menstruation in castrated women following injections of theelin. Kaufmann [9] and Clauberg [10] have gone a step further and noted menstruation in castrated women after injections of commercial preparations of the estrogenic and the corpus luteum hormone.

The important studies of Smith and Engle [11] and of Zondek and Aschheim [12] have conclusively demonstrated the dependence of the ovary on the anterior lobe of the hypophysis. If the ovary is removed the sex cycle stops, but if an excess of the hormone from the anterior lobe of the pituitary gland is added there is a marked ovarian reaction consisting of follicular ripening, ovulation and formation of corpus luteum. Zondek [13] expressed the belief that the anterior lobe has a sex factor stimulating follicular ripening and one stimulating luteinization. He designated these factors as prolan A and prolan B respectively. (In this country the term prolan is often used to designate the anterior pituitary-like hormone found in the urine of pregnant women.) Other investigators are inclined to believe that prolan A and prolan B represent quantitative variations of a single sex hormone. The process of ovulation or follicular rupture initiates the formation of the corpus luteum. Ovulation occurs spontaneously in most animals; in the cat, ferret and rabbit it occurs only after copulation. In the rabbit ovulation can be induced by injections of the urine of pregnant women and by injections of a substance obtained from the anterior lobe of the hypophysis. Normally, ovulation in the rabbit occurs from ten to twelve hours after copulation; it is thought that the act of copulation sets up a nervous impulse which stimulates the anterior pituitary lobe to secrete a hormone which produces ovulation. In human beings, ovulation occurs spontaneously. No data are available on the effect of nervous impulses on human ovulation. Under certain conditions these might become a factor. Allen [14] considered such a possibility likely. While the hypophysis has a profound action on the ovary, the ovary has a counter effect on the

7. Allen, Edgar: Contrib. Embryol. **19**:1, 1927.

8. Werner, A. A., and Collier, W. D.: J. A. M. A. **100**:633, 1933.

9. Kaufmann, C.: Klin. Wchnschr. **12**:217, 1933.

10. Clauberg, C.: Zentralbl. f. Gynäk. **57**:1461, 1933.

11. Smith, P. E., and Engle, E. T.: Am. J. Anat. **40**:159, 1927.

12. Zondek, B., and Aschheim, A.: Arch. f. Gynäk. **130**:1, 1927.

13. Zondek, B.: Die Hormone des Ovariums and das Hypophysenvorderlappens, Berlin, Julius Springer, 1931; Klin. Wchnschr. **9**:245, 1930.

14. Allen, Edgar: Sex and Internal Secretions, Baltimore, Williams & Wilkins Company, 1932, p. 431.

hypophysis. Several investigators have mentioned this interaction, notably Leonard, Meyer and Hisaw [15] and Moore and Price,[16] and it need not be considered here in detail. It suffices to say that the hypophysis stimulates the ovary, and the estrogenic factor, one of the ovarian secretions, depresses the hypophysis. Alterations in this balance could easily lead to disturbances in the menstrual rhythm. However, the complete solution of the hypophyseal-ovarian relationship is not yet at hand. The importance of this relationship in the study of endometrial hyperplasia will be considered later.

The condition known as endometrial hyperplasia has now been separated from the disorders of menstruation and stands as a clinical and pathologic entity. According to Olshausen,[17] as early as 1846 the French knew of a polypoid condition of the endometrium associated with hemorrhages. Olshausen studied the condition and gave it the name of "endometritis fungosa." Seven years later, a German gynecologist, Brennecke,[18] published the contribution which opened the way to the present day advances. He was the first to describe the absence of corpora lutea in the ovaries, and suggested that an ovarian disorder was responsible for the endometrial changes. The full significance of Brennecke's observations was not appreciated, because at that time the endometrial cycle was still unknown, and many normal conditions were described as forms of endometritis. In 1900, Thomas Cullen [19] described the condition and recognized it as an abnormal hyperplastic process of benign character, separate and distinct from endometritis. He named it "endometrial hyperplasia." However, until after Hitschmann and Adler [20] had described the normal histology of the endometrium in 1908, it was impossible to differentiate completely the normal from the pathologic process. Their work laid the foundation for the further study of endometrial lesions. This was forthcoming in the work of Schroeder [21] and to him and his pupils is due most of the credit for the present

15. Leonard, S. L.; Meyer, R. R., and Hisaw, F. L.: Endocrinology **15**:17, 1931.

16. Moore, C. R., and Price, D.: Am. J. Anat. **50**:13, 1932.

17. Olshausen, R.: Arch. f. Gynäk. **8**:97, 1875.

18. Brennecke: Arch. f. Gynäk. **20**:455, 1882.

19. Cullen, Thomas: Cancer of the Uterus, New York, D. Appleton and Company, 1900.

20. Hitschmann, F., and Adler, L.: Monatschr. f. Geburtsh. u. Gynäk. **27**:1, 1908.

21. Schroeder, R.: Arch. f. Gynäk. (*a*) **98**:81, 1912; (*b*) **104**:27, 1915; (*c*) Zentralbl. f. Gynäk. **44**:755, 1920; (*d*) in Halban, Joseph, and Seitz, Ludwig: Biologie und Pathologie des Weibes, Berlin, Urban & Schwarzenberg, 1924, vol. 3, p. 921; (*e*) Schroeder, R.; Kessler, R., and Tietz, K.: Zentralbl. f. Gynäk. **57**:11, 1933.

knowledge of endometrial hyperplasia. As a result of Schroeder's work, the Germans have recognized the condition and written voluminously about it. In England and America the condition has not commanded the attention to which it is entitled. In this country the fundamental contribution of Cullen [19] and the later work of Emil Novak [22] and Fluhmann [23] have done much to advance knowledge of the subject.

ETIOLOGY OF ENDOMETRIAL HYPERPLASIA

From a correlative study of ovarian and uterine changes Schroeder [21b] correctly inferred that the uterine changes before ovulation were caused by a hormone from the follicle, and those after ovulation by a hormone from the corpus luteum. In hyperplasia he found no corpora lutea and he concluded from this that the endometrial changes were the result of a failure of ovulation. This resulted in a persistent follicle, which stimulated the hyperplastic growth of the endometrium. The eventual cause was considered to be a disharmony of the glands of internal secretion. Meyer [24] placed a somewhat different interpretation on the ovarian findings. He considered that the stimulus arose from a succession of ripening follicles which never came to ovulation, rather than from one persistent follicle. He was unable to find any corpora lutea in his cases.

As a general rule the presence of corpora is the exception; they have been reported in only a small percentage of cases. Novak and Martzloff [25] observed corpora lutea in four cases of hyperplasia. Babes,[26] in a report from Meyer's laboratory, analyzed twenty-five cases and found corpora in three. Shaw [27] found two recently ruptured follicles and a recent corpus luteum. Fluhmann [23b] found no corpora in five instances. We believe that the occasional occurrence of corpora can probably be explained either by diagnostic errors, nonfunctioning corpora or spontaneous and induced ovulation in the course of the disease. We have recently observed three cases in which a definite hyperplasia was transformed into a normal premenstrual endometrium and normal

22. Novak, Emil: (*a*) J. A. M. A. **63**:617, 1914; (*b*) Am. J. Obst. & Gynec. **75**:996, 1917; (*c*) J. A. M. A. **75**:292, 1920; (*d*) M. J. & Rec. **130**:481, 1929; (*e*) Endocrinology **15**:273, 1931; (*f*) South. M. J. **25**:261, 1932; (*g*) in Curtis, A. H.: Obstetrics and Gynecology, Philadelphia, W. B. Saunders Company, 1933, vol. 3, p. 124.

23. Fluhmann, C. F.: (*a*) J. A. M. A. **93**:1136, 1929; (*b*) Surg., Gynec. & Obst. **52**:1051, 1931; (*c*) Endocrinology **15**:177, 1931; (*d*) Am. J. Obst. & Gynec. **21**:455, 1931; (*e*) Proc. Soc. Exper. Biol. & Med. **31**:54, 1933.

24. Meyer, R.: Arch. f. Gynäk. **113**:259, 1920.

25. Novak, E., and Martzloff, K. H.: Am. J. Obst. & Gynec. **8**:385, 1924.

26. Babes, A. A.: Arch. f. Gynäk. **122**:448, 1924.

27. Shaw, Wilfred: J. Obst. & Gynaec. Brit. Emp. **36**:1, 1929.

menstruation ensued. In each case the cervix had been stimulated by the passage of a biopsy instrument, and it is possible that the nervous stimulation from this procedure played a part in bringing about ovulation. In order for a hyperplasia to be converted into a premenstrual endometrium, ovulation and the formation of corpus luteum must have taken place. If the operation had been performed on the first or second day after ovulation, we might have obtained the picture of a hyperplastic epithelium with early corpora lutea in the ovaries. In the cases referred to had the specimens been obtained later, the epithelium might have been perfectly normal in appearance, and the expected menstruation might have been normal, as it was in our cases. These facts indicate that the hyperplastic picture may change and that ovulation and the formation of corpus luteum may terminate the disease. In such an instance there is a transitory phase in the conversion of the hyperplastic endometrium into the premenstrual endometrium. Early in this transitory phase the endometrium may be hyperplastic, and yet the condition known as endometrial hyperplasia cannot be said to exist. Spontaneous remissions have been known to all authors, and since a remission can occur only by ovulation and the formation of corpus luteum, it is not surprising that early corpora lutea have been reported in association with a hyperplastic endometrium. When mature corpora are found in the disease they are probably nonfunctioning, or there is an error in the interpretation of the endometrium. Increasing experience has confirmed our belief that endometrial hyperplasia and functioning ripe corpora lutea do not occur simultaneously.

Novak [22e] in a recent contribution stressed the importance of persistent and excessive follicular stimulation as the cause of the characteristic hyperplasia. Experimental proof of Schroeder's and Meyer's contention of an abnormal follicular stimulation producing the hyperplastic changes was put forth by Burch, Williams and Cunningham.[28] By injections of the estrogenic hormone these authors were able to produce in the endometrium of spayed rodents changes in growth which were quite similar to the changes observed in human hyperplasia. Injections of the corpus luteum hormone failed to produce such changes. Moreover, these changes were reproduced in two instances by injection of material from the cystic follicles in cases of hyperplasia. Wolfe, Campbell and Burch [29] were later able to reproduce successfully all the characteristic features of the disease in rats and guinea-pigs by injecting, over a longer period of time, a purified, crystalline estrogenic hormone,

28. Burch, J. C.; Williams, W. L., and Cunningham, R. S.: Surg., Gynec. & Obst. **53**:338, 1931.

29. Wolfe, J. M.; Campbell, M., and Burch, J. C.: Proc. Soc. Exper. Biol. & Med. **29**:1263, 1932.

theelin. On the other hand Spivack [30] was unable to produce experimental hyperplasia by injecting 10 Allen-Doisy units of a commercial estrogenic hormone every other day until fifteen doses were given. Hofbauer [31] was the first to produce the condition experimentally. He injected into guinea-pigs a substance freshly obtained from the anterior hypophyseal lobe. He considered the condition as a manifestation of an overactive anterior lobe. Oskar Frankl [32] conceded the correctness of Hofbauer's contention of overactivity of the anterior lobe for a limited number of cases but stated that local inflammatory conditions in the ovary are a far more frequent cause of hyperplasia than overactivity of the anterior lobe. Burch, Wolfe and Cunningham [33] were unable to produce the condition experimentally by utilizing Lipschütz' [34] method of partial castration, and they stressed partial castration as an important predisposing cause in human beings. It is interesting to note that of eighteen patients with endometrial hyperplasia reported on by Graves,[35] four, or 22 per cent, had had a previous unilateral oophorectomy, and that of eight patients with menorrhagia and metrorrhagia reported on by Esch,[36] three had had a previous unilateral oophorectomy.

Shaw [27] stated the belief that the primary change is in the endometrium itself, and stated:

> Thus far the explanation I have to offer to account for the features of this disease may be summarized as follows: the polypoidal endometrium reacts upon the ovaries to produce an inhibition of follicle ripening, or of ovulation or of full formation of the corpus luteum; in turn, the ovaries respond by producing continuously a toxin, identical in type with that causing the disintegration of the premenstrual endometrium in normal menstruation. In consequence, disintegration of the superficial layers of the polypoidal endometrium occurs.

Likewise, Babes [26] suggested that, in some cases, the picture may be due to a peculiarity of the epithelium itself. No experimental proof, however, has been brought forward to support these assumptions. The latest chapter has been added by Kaufmann,[9] who produced the condition in castrated women by injections of a benzoic acid ester of the dihydroestrous hormone, and one is compelled to conclude that the endometrial changes are the result of the action of the estrogenic hormone.

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30. Spivack, Mary: Surg., Gynec. & Obst. **54**:733, 1932.

31. Hofbauer, J.: Zentralbl. f. Gynäk. **54**:2569, 1930; Surg., Gynec. & Obst. **52**:222, 1931.

32. Frankl, O.: Zentralbl. f. Gynäk. **55**:68, 1931.

33. Burch, J. C.; Wolfe, J. M., and Cunningham, R. S.: Endocrinology **16**: 541, 1932.

34. Lipschütz, A.: The Internal Secretions of the Sex Glands, Baltimore, Williams & Wilkins Company, 1924.

35. Graves, W. P.: Am. J. Obst. & Gynec. **20**:500, 1930.

36. Esch, P.: Zentralbl. f. Gynäk. **54**:19, 1930.

Burch, Williams, Wolfe and Cunningham [37] pointed to a disturbance of the hypophyseal-ovarian relationship as an explanation for the abnormal production of the estrogenic substance, while Novak [22f] suggested that there is a disordered balance between the motivating hormones of the anterior lobe.

The ovarian changes have been carefully studied and, in addition to the absence of corpora lutea, the presence of follicular cysts is a prominent feature. Babes [26] estimated that there are one or two large follicular cysts in at least 60 per cent of the cases. Shaw [27] considered them an almost invariable accompaniment. The opposite ovary is shrunken and sclerotic. The cysts may be lined with a layer of granulosa cells, but frequently the latter have disintegrated. Babes [26] mentioned the scarcity of primordial follicles and the presence of degenerated ova in those present. He believed that his observations supported Meyer's theory of continuously ripening follicles rather than Schroeder's view of a persistent follicle. The cysts may attain the size of a small grapefruit and are frequently large enough to be palpated on bimanual examination. They may persist in an ovary almost indefinitely or may disappear in a few weeks. Patients have been observed in whom cysts were first noticed in one ovary, from which they disappeared only to reappear in the other ovary. The cysts are generally regarded as a manifestation of an endocrine disorder affecting the ovulatory mechanism, although some believe that thickening of the tunica albuginea can prevent ovulation in a purely mechanical way. The occurrence of the disease as a remote sequel to pelvic inflammatory conditions lends support to this view, but as yet there is no statistical or experimental evidence to confirm the theory.

The ovarian findings have not cast any light on the question of hypofunction or hyperfunction of the ovary. Most authors consider that there is a hyperfolliculism, and this implies that there is always a true increase in the amount of estrogenic substance available to act on the endometrium. It is conceivable that when there is an especially marked tendency to the production of estrogenic substance, the hypophysis is so depressed by this excess that it never reaches the peak necessary for ovulation. In the younger group of patients this may be likely. In other patients the ovary may be particularly hard to stimulate, and the production of estrogenic substance may be at a lower level than normal. In this group the hypophysis may be working at a level higher than normal, although not high enough to produce ovulation in the refractory ovaries. This seems likely in some of the older patients. No histologic criteria indicating the degree of secretion of the estrogenic hormone

37. Burch, J. C.; Williams, W. L.; Wolfe, J. M., and Cunningham, R. S.: J. A. M. A. **97**:1859, 1931.

have been developed, and the question of hypersecretion and hyposecretion of that hormone must be settled by the results obtained from quantitative studies of the blood throughout the course of the disease.

No data on the histologic changes in the pituitary gland in human hyperplasia have been encountered. Wolfe, Phelps and Cleveland [38] studied this question in rats and guinea-pigs subjected to extreme partial castration. Some of the animals failed to come into estrus after the operation; in such animals the pituitary gland showed an increase in the number and size of the basophilic cells, which became modified into castration cells. In other animals continuous estrus, associated with hyperplasia of the endometrium, was observed. The anterior pituitary lobes of such animals exhibited a decrease in the relative percentage of basophils; the basophils present contained little granular material. The full significance of these findings is not apparent, but they show clearly that different ovarian conditions are reflected in the histologic structure of the anterior pituitary lobe.

The relation of the thyroid gland to hyperplasia has often been suggested, largely on account of the successful use of thyroid extract in an occasional case. Opinion, however, is divided on this point, largely as a result of insufficient data. Owing to the relative rarity of the juvenile types, in which the point is of the utmost importance, and to the great frequency of the menopausal types, in which glandular therapy is rarely considered, large series of basal metabolic rates are not available. Gyllensvärd [39] noted the question of whether a disturbance of thyroid function may not be a cause of the disease in the adolescent groups. He reviewed the previous work of other authors and reached the conclusion that, even though it must be regarded as probable that in a few cases there is a disturbance of thyroid function, such a disturbance cannot, at least with the present methods of investigation, be demonstrated in a sufficiently large number of cases to be justifiably regarded as the cause of the hemorrhages. The evidence regarding the part played by the thyroid gland in menstrual disorders has been well summarized by Mazer and Goldstein.[40] They found the basal metabolic ratio below minus 15 in only four of one hundred and three cases. Sehrt,[41] McCarrison [41] and Bram [41] expressed the belief that menorrhagia is a symptom of hypothyroidism. Warfield,[41] however, stressed the infrequency of men-

38. Wolfe, J. M.; Phelps, D., and Cleveland, R.: Anat. Rec. **55**:85 (supp., March 25) 1933.

39. Gyllensvärd, N.: Acta obst. et gynec. Scandinav. **11**:423, 1931.

40. Mazer, C., and Goldstein, L.: Clinical Endocrinology of the Female, Philadelphia, W. B. Saunders Company, 1932.

41. Quoted by Mazer and Goldstein.[40]

strual disorders in hypothyroidism. The ultimate solution of this question awaits further clinical research on proved cases of endometrial hyperplasia.

From time to time there have been reported cases in which menstrual disorders have been attributed to nervous causes. Novak [22a] reported two cases and Miller [42] presented an exceedingly interesting series of cases illustrating this point. At the present time we have a similar case under observation. The relationship of ovulation to nervous stimulation has already been discussed, and the possibility of a nervous factor in the production of the disease is admitted, but so far proof of its occurrence is lacking.

Since hyperplasia is closely connected with disorders of the hypophyseal-ovarian relationship, it is not unreasonable to expect tumors of the hypophysis and proliferating tumors of the ovary to be associated with the disease.

According to Henderson,[43] adenomas of the pituitary gland produce sexual dysfunction as a result of compression of the normal portion of the gland. The two common types of adenomas, acidophilic and chromophobic, do not differ in the type of sexual dysfunction produced. The sex hormone is considered as being derived from the basophilic cells. Basophilic adenomas are less common than acidophilic and chromophobic, and no reference to them in connection with endometrial hyperplasia has been noted.

While tumors of the pituitary gland are not related to the disease, the relationship of proliferative tumors of the ovary to endometrial hyperplasia is well established. On several occasions Schiffmann [44] called attention to these tumors. He considered the endometrial changes to be the result of a hormone produced in the tumor, while Oscar Frankl,[45] in reporting a fibroma associated with endometrial hyperplasia, stressed the possibility of the mechanical disturbance of circulation creating a stimulus for endometrial growth. Some of the earlier authors mentioned that congestion may provide a stimulus for endometrial growth. While this general assumption has not been disproved, most authors consider that the stimulus from proliferative tumors is due to a hormone and not to passive hyperemia resulting from the tumor. Schuschania's [46] observation of the estrogenic hormone in the blood and urine of one patient supports this contention. As regards type, granulosa cell tumors, Brenner's tumors, fibroma, carcinoma and sarcoma have all been mentioned. Mistakes in classification have been frequent, and the present

42. Miller, J. A.: M. J. & Rec. **134**:84, 1931.
43. Henderson, W. R.: Endocrinology **15**:111, 1931.
44. Schiffmann, Josef: Arch. f. Gynäk. **150**:159, 1932.
45. Frankl, O.: Zentralbl. f. Gynäk. **53**:9, 1929.
46. Schuschania, P.: Zentralbl. f. Gynäk. **54**:1924, 1930.

tendency is to classify most of these tumors in the group of granulosa cell tumors. The appearance of the tumor after the menopause produces somewhat of a sexual regeneration. The endometrium is hyperplastic, and irregular bleeding occurs. Ovarian tumors associated with postmenopausal hyperplasia are always suggestive of malignancy. Schiffmann [44] and TeLinde [47] stressed the practical importance of this association. The latter's excellent contribution has done much to arouse interest in this subject.

Studies on the hormone content of the blood and urine of patients with endometrial hyperplasia are suggestive, but they are of significance only when they include a comparison with the normal. Since the almost simultaneous discovery by Frank [48] and by Lowe [49] of estrogenic substance in the circulating blood of normal women, fairly definite normal values have been established. Considerable work on this subject has been done by Frank and his collaborators.[50] These investigators worked out a more or less standardized test for the determination of the presence of the estrogenic factor in the blood which is of importance in the diagnosis of certain gynecological conditions. Briefly, their findings in a large series of normal women were as follows: Demonstrable amounts of estrogenic substance were found in the circulating blood in the premenstrual phase of the menstrual cycle. In a few instances the substance was found as early as ten days before the onset of the next menstrual period; [50c] in practically all the women it was found in the blood three days before the expected menstruation. At the onset of menstruation the estrogenic substance disappeared rapidly from the circulating blood, but was found highly concentrated in the first blood of the menstrual discharge.[50c] These pioneer studies of Frank and his co-workers have been subsequently confirmed by others, notably by Mazer and Hoffman,[51] Mazer and Goldstein,[40] Hirsch [52] and Siebke.[53]

In a recent and important contribution Fluhmann [23e] described the utilization of the methods of Robson and Wiesner [54] and of Meyer and Allen [55] (who found that a subcornifying dose of estrogenic hormone resulted in mucification of the vaginal mucosa of spayed mice) as a

47. TeLinde, R. W.: Am. J. Obst. & Gynec. **20**:552, 1930.

48. Frank, R. T.; Frank, M. L.; Gustavson, R. G., and Weyerts, W. W.: J. A. M. A. **85**:510, 1925.

49. Loewe, S.: Klin. Wchnschr. **4**:1407, 1925.

50. Frank, R. T.: (*a*) The Female Sex Hormone, Springfield, Ill., Charles C. Thomas, Publisher, 1929; (*b*) J. A. M. A. **97**:1852, 1931; (*c*) **90**:106, 1928.

51. Mazer, C., and Hoffman, J.: Am. J. Obst. & Gynec. **17**:186, 1929.

52. Hirsch, H.: Arch. f. Gynäk. **133**:173, 1928.

53. Siebke, Harold: Zentralbl. f. Gynäk. **53**:2450, 1929.

54. Robson, J. M., and Wiesner, B. P.: Quart. J. Exper. Physiol. **21**:217, 1931.

55. Meyer, R. K., and Allen, W. M.: Science **75**:111, 1932.

test for that hormone in the blood of normally menstruating women. In his experiments he injected fresh blood serum into spayed mice, which were killed on the third or fourth day after the first injection. The vaginae were fixed and sectioned. In mice which had received serum containing a detectable amount of estrogenic substance the vaginal epithelium was mucified. In his total series he tested the blood of fifty-seven women during the different phases of the menstrual cycle. The blood of ten women in the early proliferative stage, from the fourth to the seventh day of a thirty day cycle, was examined; two tests were positive and eight negative. Nine of fifteen tests made in the late stage of proliferation were positive; fifteen of eighteen tests made in the early phase of secretion were positive, and six of seven tests made in the last stages of secretion were positive. The blood of three women within forty-eight hours of menstruation was examined; only one test was positive. These results seem to be of special importance; they compare well with the findings of Frank and his co-workers; also they offer a more exact method for the determination of small amounts of estrogenic substance than does cornification of the vagina. It is to be hoped that this excellent method of study will be extended to abnormal conditions.

The estrogenic substance has also been detected in the urine of normally menstruating women. Frank [50b] found that normal women may secrete from 800 to 1,500 mouse units of that substance during one menstrual cycle; two periods of maximum excretion were found, one near the time of ovulation and the other one or two days before menstruation. Kurzrok and his collaborators [56] reported that normal women secrete from 10 to 20 units of estrogenic substance per liter of urine. They found little variation in the amount secreted during the various phases of the menstrual cycle.

Since endometrial hyperplasia appears as the result of an abnormal stimulus in the secretion of estrogenic substance several investigators have tested the blood and urine of patients with this condition for the presence of the hormone, but the results have been somewhat variable. Frank [50b] studied several groups. In a series of over a dozen adolescents with endometrial hyperplasia he found that both the urine and the blood contained an excess of estrogenic hormone. He also reported that the blood of women showing climacteric bleeding of a functional type exhibited a high level of that hormone; in some instances some cyclic variation in the amounts present was noted. The endometrial changes were closely similar to those in the pubertal group. In contrast, he failed to find such high levels of estrogenic substance in the blood of adult patients exhibiting functional menorrhagia and metrorrhagia. Occasionally the

56. Kurzrok, R.; Boylan, James; Goldman, S., and Creelman, M.: Endocrinology **16**:361, 1932.

blood of these patients contained small amounts of the hormone, which, in such instances, exhibited cyclic variations. The endometrium of the aforementioned adult patients was either of the resting or of the stationary hyperplastic type. Mazer and Goldstein,[40] in agreement with Frank, failed to find the estrogenic substance in the blood of mature women with dysfunctional uterine bleeding. Furthermore, in contrast to Frank, they failed to find the substance in the blood in a high percentage of cases of adolescent girls suffering from the bleeding of puberty. They demonstrated its presence in the blood in only four of fifteen patients with functional preclimacteric bleeding. (These investigators reported no observation on the endometrium.) Siebke,[53] utilizing the method of Frank and Goldberger, studied the blood of sixteen patients with glandular hyperplasia of the endometrium. In ten instances the blood contained the estrogenic principle; in these cases the patients were not bleeding or had been bleeding for only a relatively short period. In nine observations made on the blood of patients who had been bleeding for a longer period (from two and a half weeks to three months) no estrogenic substance was found in the blood. Zondek [57] found the substance in the urine of patients during the amenorrheic periods of "hyperhormonal amenorrhea." The ovaries of these patients showed follicles which exceeded normal follicles in size and hormone content. In patients exhibiting polymenorrhea, usually associated with cystic hyperplasia of the endometrium, Kurzrok and his associates [56] found that as much as 60 units of estrogenic substance per liter of urine sometimes occurred. On the other hand, Mazer and Hoffman [51] failed to find the hormone in the urine of six patients exhibiting endometrial hyperplasia. (They used unconcentrated urine and failed to relate the time of collection of the sample to the time of the bleeding.)

Since the studies of Hartman, Firor and Geiling [5] called attention to the fact that a factor from the anterior lobe of the pituitary gland might be concerned as a direct etiologic agent in the induction of uterine bleeding, several investigators have studied the blood and urine of normally menstruating women for the presence of a hormone or hormones of the anterior lobe of the hypophysis. Frank, Goldberger and Spielman [58] demonstrated that the ovarian stimulating factor or factors of the anterior lobe may be found in the circulating blood of normally menstruating women. They found the greatest amounts during the early period of the cycle from the sixth to the ninth day following the onset of the previous menstruation. Neumann and Peter,[59] on the other hand,

57. Zondek, B.: Zentralbl. f. Gynäk. **54**:1, 1930.

58. Frank, R. T.; Goldberger, M. A., and Spielman, F.: Proc. Soc. Exper. Biol. & Med. **28**:999, 1931.

59. Neumann, H. O., and Peter, F.: Klin. Wchnschr. **10**:2086, 1931.

found the hormone from the anterior lobe most abundant during the premenstrual phase. The factor from the anterior lobe has also been found in the urine of normal women. Zondek [60] found a maximum secretion of this hormone just before menstruation; there was a fall directly after menstruation. Katzman and Doisy,[61] studying the urine of normally menstruating women for the presence of the hormone from the anterior lobe found that urinary excretion was high at the time of ovulation and during menstruation.

The studies cited serve as controls for studies concerned in determining the possible presence of hormone or hormones from the anterior lobe in the blood or urine of patients with endometrial hyperplasia. Fluhmann [23b] examined the blood of ten patients with endometrial hyperplasia; only one showed the presence of the hormone. Mazer and Goldstein [40] were unable to find the hormone of the anterior lobe in the blood of eight young women with functional menorrhagia. (No endometrial observations were made.) Fluhmann [23c] described a group of patients which he termed "hypohormonal." This group consisted of young women with polymenorrhea and women near the menopause exhibiting too profuse and too frequent menses. These patients showed pituitary factors from the anterior lobe in their blood. Although such patients may show endometrial hyperplasia, Fluhmann is of the opinion that this is not generally the rule. It was proved that two of the patients who exhibited hypophyseal factors from the anterior lobe in the blood did not have endometrial hyperplasia. It seems fairly clear from the studies presented that endometrial hyperplasia is not associated with the presence of pituitary factors from the anterior lobe in the blood.

On the other hand, patients who exhibit a definite hypo-estral condition may exhibit large amounts of pituitary factors from the anterior lobe in the blood. Fluhmann [23c] found such factors in the blood of castrated women after the menopause and in cases of amenorrhea of long standing.

Smith and Rock [62] studied the urine of patients with menorrhagia and metrorrhagia. They found that fourteen of eighteen specimens collected during the period of bleeding contained a substance which produced follicular ripening when injected into immature rats. In the nonbleeding groups eleven of thirteen specimens were completely negative.

THE TISSUE CHANGES

The changes in the endometrium are the result of an excessive proliferation resulting from an abnormal estrogenic stimulus. In considering these changes it seems essential to show their relation to and their

60. Zondek, B., quoted by Katzman and Doisy.[61]

61. Katzman, P. A., and Doisy, E. A.: Proc. Soc. Exper. Biol. & Med. **30**: 1188, 1933.

62. Smith, G. V., and Rock, John: Surg., Gynec. & Obst. **57**:100, 1933.

point of departure from the normal. In describing the condition we shall first trace the endometrium through the postmenstrual and interval phases into the hyperplastic state. In the postmenstrual phase the endometrium is thin and pale. The thickness varies between 0.5 and 0.9 mm., and the surface is smooth. The few slender, cylindric glands expand gradually from the surface and follow a wavy course to the muscularis. The epithelium is composed of low, narrow cylindric cells, the inner borders of which are smooth and well defined. The cytoplasm is scanty, of a homogeneous consistency and acidophilic. Some of the cells have cilia. The nuclei stain deeply, may be round but are usually oval, and occupy a basal position. Mitoses are at first infrequent but increase throughout the postmenstrual and interval phases. There is no sign of secretion in the cells or in the lumens of the glands. The stroma cells are spindle-shaped or oval. The cells in the superficial portions are arranged more loosely than in the deeper. The nuclei stain deeply and almost fill the cell. There are little edema and few polymorphonuclear leukocytes. The glands increase in length and their lumens widen as the postmenstrual phase merges into the interval phase. Both phases are characterized by a proliferation of the endometrial elements as a result of the estrogenic stimulus. The terms are retained only on account of their general use. It would be better if they were eliminated and the term "proliferative phase" or "estrogenic phase" substituted. In the latter half of the proliferative phase (the old interval phase) the glands increase in length and their lumens widen. The glands open through a narrow neck, and they expand basally in a somewhat uniform manner. A rare gland may show no expansion of the lumen. Occasional glands may show cystic or fusiform dilatation while others are oval. The growth of the glands is more rapid than the growth of the stroma, and this produces the characteristic sinuous form. The number of glands is increased, probably by the growth of basal buds from the lamina basalis to the surface. O'Leary,[63] who was the first to mention these structures, described them as follows:

> From the portions of the glands surrounded by the denser fibroblastic stroma of the lamina basalis, vertical tubules arise which project for varying distances into the stroma of the functional layer and which have no connection with the surface. However, since they reach a much greater length in older mucous membranes, we may assume that they eventually reach the surface and establish new glands, thus serving to increase the number of glands in the later stages. Mitoses in these structures indicate that they are actively growing.

Late in the proliferative phase some glands are dilated and filled with a coagulated material, which is faintly positive to mucicarmine. This material is not of the same appearance or character as the mucoid

63. O'Leary, J. L.: Am. J. Anat. **43**:389, 1929.

secretion seen in the premenstrual phase, and its relation to the latter is not as yet clear. Bartelmez [64] suggested that there are two phases of secretion in the menstrual cycle, the first characteristic of the early interval, the second characteristic of the premenstruum. During the interval there is little intracellular secretion, and the cells are higher and broader. They are somewhat crowded together, giving an appearance of pseudostratification. The cytoplasm is increased, and the nuclei stain deeply. Mitoses are frequent. The inner cell border may lose its sharp outline and assume a fringed appearance. Glycogen is said to be absent. Superficial edema of the stroma may be present.

In hyperplasia the fundamental tendency is a continuation of growth. It is a growth which exceeds normal bounds. Some specimens show marked evidence of this excessive growth while in others it is less marked. In fact it is often difficult to determine from histologic appearances alone where the normal ends and the abnormal begins. Mack [65] studied the degree of hyperplasia in two hundred specimens and found that it was circumscribed in 15, mild in 24, moderate in 49, strong in 10 and very strong in 2 per cent.

In the mild cases there is an absolute increase in the number of glands and of cells. As a result there is a certain irregularity of pattern that stands out in contrast to the normal. There are minor variations in the course of the glands; some are straight, some saw-toothed, and some sinuous. Occasionally, bizarre forms are seen. Variations in the size of the lumens are apparent; a few cystic glands are scattered throughout the endometrium. In some glands the epithelium is single-layered; in others it is denser and often pseudostratified, so that the epithelium has a thick, massive appearance. Epithelium of all kinds may be found in the cystic glands. Frequently it is flattened. Mitoses are commonly seen in good preparations. The vessels are moderately large and engorged with blood; they extend throughout the whole thickness of the epithelium. The stroma is markedly variable. In some areas it is thick; in others, thin. Mitoses are found rather commonly in the connective tissue cells of the stroma. Edema is commonly observed and varies in different parts of the same section. It is to be looked on as a manifestation of circulatory stasis, and in arriving at a conclusion regarding the state of the specimen the edematous areas should be excluded as abnormal and only the nonedematous areas judged. Under the surface epithelium there may be dilated veins surrounded by an area of edema or hemorrhage. The presence of venous thromboses surrounded by areas of necrotic tissue is an important and characteristic finding.

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64. Bartelmez, G. W.: Anat. Rec. **35**:3, 1927.
65. Mack, Harold: Zentralbl. f. Gynäk. **53**:2068, 1929.

In severe cases, the size of the glands is more variable. The larger glands are cystic, and some are as large as a low power field. Marked variations in shape are noted. Seen in cross-section some are practically round; others have large scallops fairly regular in size. Still others have rounded or pointed projections into the lumen. Longitudinal sections show similar variations of a less extreme variety. These variations in the size of the gland lumens produce the well known "Swiss cheese" appearance to which Novak called attention. The glandular epithelium is very dense at points. In some areas there are two or more layers of cells. The nuclei of the inner layer of cells are flattened, and those of the outer are round or oval. In other areas there seems to be only one layer of cells, but these are so crowded together that they exhibit a pseudostratified appearance. The location of the nuclei varies; some are central and some are basal. The nuclei are flattened and cigar-shaped, and appear to touch each other. Some are wedge-shaped from pressure. Mitoses are frequently seen in good preparations; in poorly fixed specimens they are difficult to find. The inner cell borders are usually clear and distinct, but sometimes they are ragged and seem to be crumbling away. In many cases the lumens of the glands are absolutely empty; in others they contain a variable amount of coagulated material and cellular débris. Occasional cells with distinct pyknotic nuclei and an abundance of granular cytoplasm are present in the lumens. The stroma undergoes the same variations as seen in the milder cases, except that the capillaries are fuller and the veins more dilated.

The presence of areas of necrosis is of considerable importance. Schroeder,[21b, d] stressed the frequent occurrence of these areas and their importance in the development of bleeding. According to him the primary change in the development of these areas is a stasis of blood in the thin-walled, dilated vessels. This brings about disturbances in the nutrition of the surrounding tissue, resulting in areas of edema, areas of hemorrhage and areas of necrosis. Fluhmann [23a, b] found necrotic areas in a high percentage of cases and, like Schroeder, he considered them of great importance. He quoted the work of Mikulicz Radecki who, by means of a viewing instrument or hysteroscope, noted hemorrhages from isolated vessels and defects in the endometrium. The latter were noted especially in cases of endometrial hyperplasia. Other authorities, notably Novak, have considered the necroses of less importance. Novak [22f] stated:

> It has always seemed to me that these areas, often very small, can hardly be looked upon as the source of the often extremely profuse bleeding exhibited by these patients, and that some local biological factor must be present in the endometrium, increasing the permeability of its blood vessels. This seems likely in view of the frequent gross intactness of the mucosa, even when the bleeding has been profuse and prolonged.

In another article [22g] he expressed the following opinion: "One cannot, as a matter of fact, be sure that the necrotic areas are not the result rather than the cause of the bleeding." In our own patients we have frequently noted the occurrence of these areas of necrosis, and we believe that they are in some way connected with the process of bleeding.

FACTORS IN THE BLEEDING

The bleeding of the hyperplastic endometrium is due in some instances to factors other than the hyperplasia, as patients have been observed who had a hyperplastic endometrium yet did not exhibit bleeding. In fact, we have recently found an endometrial hyperplasia in the uterus of an 8 months fetus. On the other hand, there are certain distinct anatomic differences between the bleeding processes originating in the normal endometrium and those originating in the hyperplastic endometrium. In normal menstruation the necrosis affects the entire mucous membrane, and the separation of the necrotic layer takes place within from twenty-four to forty-eight hours. After the necrotic area has been cast off, the basalis lies open, and bleeding occurs from the stumps of the vessels. This bleeding from the basal layer is rarely severe and stops within a short while. In the hyperplastic mucous membrane the necrosis occurs in small, widely separated areas and gradually extends so that even two or three months may elapse before desquamation takes place. In fact desquamation of the epithelium down to the basal layer may never occur. In the hyperplastic epithelium, as in the normal, bleeding stops promptly when the endometrium is removed with the curet and the basalis is exposed. It seems, therefore, that the failure of the endometrium to undergo proper desquamation is an important factor in the profuse bleeding. Whether this is due to the great anatomic differences between the normal and the hyperplastic endometrium or to a derangement of some common factor governing desquamation is not clear at present. Graves [35] made the following interesting observation in this connection:

> A study of uterine blood in functional metrorrhagia was initiated by making daily examinations of the discharge from a girl of 23 with long standing idiopathic hemorrhage. Later biopsy from curettage revealed a marked gland dysplasia. Microscopic examination failed to show the characteristic endometrial remnants seen in normal menstruation. This single observation taken in conjunction with the nearly universal occurrence of clotting in our cases supports the conclusion otherwise logical, that the blood in dysfunctional hemorrhage is deficient in or entirely lacks the secretory elements that would be evidenced by a normal corpus luteum. In other words, it approaches or may be equivalent to an ordinary body hemorrhage according to the extent of the functional disturbance. This probably explains the severe and uncontrollable hemorrhages that are frequently encountered.

The factor of traumatism as a cause of bleeding has been mentioned by Seitz,[66] and this undoubtedly plays a rôle in cases in which a hyperplastic mucous membrane comes in contact with a submucous fibroid. Whether contact between the endometrium on the anterior and posterior walls plays a rôle has not been mentioned. We have noted this contact in cases of hyperplasia and have seen areas of hemorrhage on both sides at the point of contact. It is also not inconceivable that sudden increases in intra-abdominal pressure may cause a rupture of one of the thin-walled superficial veins. Since the endometrium is directly under the control of the ovaries and the ovaries are under the control of the anterior lobe of the pituitary gland, investigators have looked to these organs for an explanation of the endometrial changes. As previously mentioned, Shaw [27] advanced the opinion that the cause of the disintegration of tissue in the hyperplastic endometrium is a toxin produced in the ovaries. He further held that the disintegration of tissue is almost identical in its histologic features with that occurring during menstruation. Burch and Burch [67] suggested abnormal and irregular declines in estrogenic substance as the causative factor for the long continued bleeding. It is apparent that there must be a point at which the amount of estrogenic hormone ceases to be sufficient to maintain the endometrium. If the amount necessary for maintenance is barely present, it is not inconceivable that necrosis may occur at points of lesser circulation. These points would reasonably be in the periphery of the tissue or close to the surface, and localized instead of generalized necrosis would occur. If the decline in estrogenic hormone should be of long duration and slight degree other areas would be slowly involved, and a process not unlike that seen in hyperplasia would result. Siebke's [68] demonstration that estrogenic substance is present in the blood of patients with hyperplasia in the interval and early stages of bleeding but not in the late stages of bleeding is of especial importance in this connection. The results of Smith and Rock [62] suggest that the hormone, like that from the anterior hypophyseal lobe, which they found in the urine of patients with hyperplasia during the period of bleeding only may be associated with the etiology of the condition. Novak and Hurd [69] expressed the opinion that the bleeding is determined by a bleeding factor which is still unknown, but which appears to be bound up in some way with a disturbance in the balance between the follicle-stimulating hormone from the anterior lobe and the luteinizing hormone.

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66. Seitz, A.: Arch. f. Gynäk. **116**:252, 1922.
67. Burch, L. E., and Burch, J. C.: Am. J. Obst. & Gynec. **25**:826, 1933.
68. Siebke, H.: Arch. f. Gynäk. **146**:417, 1931. Siebke.[53]
69. Novak, E., and Hurd, G. B.: Am. J. Obst. & Gynec. **22**:501, 1931.

Fibroid tumors are generally considered to be a common cause of uterine bleeding, and every pathologist has seen many cases in which the fibroid was clearly responsible for the bleeding. In a definite percentage of cases, the tumor is small, subserous or intramural and produces no visible alteration in the endometrium. Nevertheless bleeding is present and is so severe as to demand operation. In many other cases there is a well marked hyperplasia in the endometrium with a definite fibroid in the myometrium. In such instances one is inclined to consider the hyperplasia as the cause of the bleeding and the fibroid as a more or less unimportant accompaniment. Cases of this kind are commonly observed. King [70] in a recent article stated:

> Another fact of interest bearing on the clinical side of hyperplasia is its frequent association with fibroid tumors. This is a matter of common observation, but there is as yet no adequate explanation to account for it. Its frequency would surely exclude its being a chance relationship. It is more commonly found in connection with the smaller tumors, as the larger ones by stretching and pressure are likely to produce endometrial atrophy. In a series of 114 fibroids treated by radium, I found that 81, or 71 per cent showed hyperplasia. The practical point in this connection is that bleeding associated with many of these tumors is undoubtedly due to the presence of hyperplasia and not primarily to the fibroid. A further suggestive fact is found in the frequent combination of endometrial and myometrial hyperplasia, and the clinician awaits with interest any forthcoming explanation.

Witherspoon [71] has discussed the rôle of ovarian dysfunction, resulting in follicular cysts, as a possible factor in the causation of fibroids. He reasoned that the abnormal estrogenic stimulus affected not only the endometrium but the myometrium as well. Since fibroids grow slowly, he concluded that an abnormal estrogenic stimulus would produce an immediate hyperplasia and gradually developing fibroids. In a further study Witherspoon and Butler [72] investigated one hundred and twenty-five cases of fibroids in Negro women. The facts derived from their study tend to support Witherspoon's hypothesis. They expressed the opinion that the enormous incidence of pelvic inflammatory disease in the Negro produces hyperplasia as a result of inflammatory changes in and around the ovary. The same stimulus which produces the hyperplasia likewise produces the myometrial growth. Clinically, the association of fibroid and hyperplasia is of extreme importance. Unless it is definitely determined which is responsible for the bleeding, the patient may receive treatment for one and be suffering from the other. Under certain conditions the treatment of the two is essentially different, and if this point is borne in mind many proposed operations will prove unnecessary.

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70. King, James E.: Am. J. Obst. & Gynec. **26**:582, 1933.

71. Witherspoon, J. Thornwell: Surg., Gynec. & Obst. **56**:1026, 1933.

72. Witherspoon, J. T., and Butler, Virginia: Surg., Gynec. & Obst. **58**:57, 1934.

From a practical standpoint the diagnosis of endometrial hyperplasia is of extreme importance; it is not always easy, and even in the best laboratories the percentage of errors is high. Taylor [73] made the following statement concerning the experience at the Roosevelt Hospital:

> The work of reviewing the microscopic material had scarcely begun when it became clear that the problem, at least so far as the Roosevelt Hospital was concerned, depended upon the correction of diagnosis by the definition of the morphologic characteristics of glandular hyperplasia and its clear separation from physiologic forms of hypertrophy on the one hand and from early carcinoma on the other.
>
> During the five year period, 1925-1929, the diagnosis of hyperplasia or hypertrophy, or the apparently synonymous terms, hyperplastic or hypertrophic endometritis, were applied to 257 specimens of which, after extensive resectioning of material, 216 were available for satisfactory microscopic review. Of this number only 88 would probably be classed as glandular hyperplasia.

Taylor used the term "glandular hyperplasia" in reference to the endometrial changes which we have described as endometrial hyperplasia. After reviewing our own series, we can confirm his observations. In our opinion the main difficulty has been in the use of the term "hyperplasia." The endometrium is a constantly changing tissue, and it is difficult to define the exact line at which the normal ends and the pathologic begins. In the sense that hyperplasia is an abnormal multiplication of tissue elements, it is apparent that such a process could affect any of the elements of the endometrium at any phase of the cycle. Therefore in reviewing a series of cases we find that the diagnosis has been made because there is a thick stroma, an exceptionally large number of glands or an abnormal multiplication of cells. These changes may have occurred in any of the phases of the cycle and in patients who were menstruating normally as well as in those menstruating abnormally. In the sense in which we have employed the term in this article it is limited to patients exhibiting an abnormal increase in the elements of the endometrium, an absence of functioning corpora lutea and a profuse and irregular hemorrhage.

However, experience has shown that in many cases of pathologic bleeding little increase in the elements of the endometrium can be demonstrated. In some cases in which the specimen has been obtained at the end of a long period of bleeding one finds an endometrium similar to that seen in the interval phase. It is true that it is hyperplastic in the sense that it is further advanced in the cycle than it should be. Yet it is similar to other specimens which, from the morphologic point of view alone, are considered normal. In still other specimens the bleeding originates in an endometrium corresponding in time relations and histology to the type seen in the interval phase. These patients do not

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73. Taylor, H. C. Jr.: Am. J. Obst. & Gynec. **23**:309, 1932.

exhibit hyperplasia in the sense of an abnormal multiplication of tissue, yet there is an absence of corpora lutea as evidenced by the absence of progestational changes. While they do not exhibit the advanced morphologic changes of hyperplasia, clinical and experimental facts indicate that the changes shown are different forms of the same process and are to be classified with it. The presence of an estral hyperplasia of the endometrium is therefore not absolutely essential to the diagnosis of "endometrial hyperplasia."

The absence of corpora lutea can be determined with certainty only from an examination of the ovaries. Since the retrogression of the corpus luteum requires several months, an ovary may contain several corpora and yet have none corresponding to the present cycle. A knowledge of the life history of the corpus luteum is therefore essential in determining whether the corpora are retrogressing or not. Nonfunctioning or deficiently functioning corpora are theoretically possible. They occur in the rat and mouse. No data are available on this point in regard to human beings. A failure to function would manifest itself by a continuation of the interval type of endometrium and an absence of progestational changes. In the vast majority of cases the ovaries are not available for pathologic examination, and the presence or absence of functioning corpora must be established by the endometrial changes. If progestational changes are present, functional corpora lutea are present; if progestational changes are absent, functional corpora lutea are absent. These progestational changes affect the whole endometrium but are best observed in the glandular epithelium. The cell surface projecting into the lumen appears ruptured or frayed as if melting away into the mucoid secretion in the lumen of the glands, which has a strong affinity for mucicarmine. The cells are wider and broader than in the interval, and hence the nuclei are farther apart. The increase in the volume of the cell results in projections of the epithelium toward the lumen. In these projections the nuclei appear crowded together while in the nonprojecting portions the nuclei tend to be round and assume a basal position. These round, widely separated, basal nuclei give to the tissue a regular, orderly appearance which stands out in contrast to the piled up, rapidly growing cells of the interval. The cytoplasm loses its staining reaction and diminishes in volume. The compact, spongy and basal layers are well defined. In the compact layer one may occasionally find well developed decidual cells. If these progestational changes are present, one is not dealing with endometrial hyperplasia. Before this diagnosis can be established it is essential that the bleeding originate in an endometrium which reflects only the changes produced by the estrous hormone. We have designated this as an "aluteal endometrium."

The pathologist is, of course, dependent on the clinical history for the facts relating to the abnormal bleeding. Many gynecologists still seem to think that hyperplasia is a constant, definite, morphologic condition with stationary characteristics. They fail to realize that in many cases belonging to the hyperplasia group the endometrium shows little deviation from the normal interval type. The abnormality is not in the changes exhibited by the endometrium but in the lack of conformation to the type from which normal bleeding usually occurs. Excessive bleeding from any type of endometrium is pathologic. Any type of bleeding from an aluteal type is unusual; when excessive it is pathologic, and it is this condition of excessive bleeding originating in an aluteal endometrium which should be designated as endometrial hyperplasia. It is the function of the pathologist to determine the type and characteristics of the endometrium, and it is the function of the clinician to determine the type and character of the abnormal bleeding. Only by taking into account the information obtained by both can the diagnosis be established. When these facts are generally realized and every specimen of endometrium is accompanied by a careful and thorough menstrual history, the diagnosis of endometrial hyperplasia will be simplified and information obtained for further advances in the study of the sex cycle.

DIAGNOSIS

Our own studies have shed some light on the difficulties of diagnosis. It soon became apparent that it would be impossible to study hyperplasia in the same patient throughout several weeks if we were to depend on repeated curettings for our material. Moreover, in addition to the necessity for hospitalization and anesthesia, the procedure was found impractical, owing to the resulting disturbance of the cycle and the difficulty of evaluating the rate of regeneration of endometrial tissue. Klingler and Burch [74] developed a method which partially overcame these difficulties. It consisted in applying suction to the uterine mucosa by a cannula inserted through the cervix. The cannula had a simple opening at the end and was of the size of an ordinary uterine sound. Suction was obtained by means of an attached syringe. With this arrangement it was possible to obtain small bits of tissue. The procedure caused little pain and could be carried out in the office or dispensary. By the use of this method we obtained serial specimens of tissue from the same patient. The suction method was not entirely satisfactory, however, and the attention of one of us (Dr. Burch) was directed to the possibility of improving it by the intra-uterine use of the ordinary cup specimen forceps. Owing to the intelligent and skilful

74. Kingler, H., and Burch, J. C.: J. A. M. A. **99**:559, 1932.

cooperation of the instrument maker [75] an intra-uterine forceps has been made which is entirely satisfactory. The cup is about the size of the bulbous end of an ordinary uterine sound, and since it is mounted on a flexible shaft, it can be inserted as easily as a sound. The biting out of the endometrium is about as painful as an ordinary pinch. The cup usually holds the material obtained from two bites of the forceps, and at each insertion of the instrument two specimens of tissue from different areas may be obtained. The procedure is carried out in the office or dispensary, and patients have been followed for as long as two or three months. In addition to its usefulness as a means of study, the intra-uterine biopsy method has done much to eliminate the use of the curet as a diagnostic instrument. By taking biopsies at frequent intervals in the course of the disease we have been able to obtain considerable information. Hyperplasia has been noted before, during and after a spell of abnormal bleeding; yet ovulation subsequently took place, the hyperplastic endometrium was transformed into a normal premenstrual endometrium, and a normal menstruation ensued. The presence of hyperplasia does not, therefore, exclude the possibility of a subsequent ovulation, the formation of a premenstrual endometrium and normal menstruation, unless the specimen was obtained at or very near the onset of bleeding. For this reason, we advocate the taking of specimens as near the onset of bleeding as possible. This will do much to eliminate errors in diagnosis.

Grossly the appearance of the hyperplastic endometrium is somewhat characteristic. There are long polyp-like and fungous growths projecting into the cavity. The fungous appearance may suggest carcinoma. Often the tissues show numerous hemorrhages between which are areas of normal endometrium. The thickness may be as much as several centimeters. Careful examination will often reveal the presence of many small, clear vesicles. These are characteristic. In addition there is no infiltration of the muscle. Experienced observers can usually exclude carcinoma by the presence of vesicles and the absence of infiltration. Occasionally this is impossible and the question has to be settled by a microscopic examination.

Since hyperplasia and cancer are both proliferative processes, it is not unnatural that a possible relationship between the two should have been suspected, and it is, in fact, sometimes difficult to distinguish between carcinoma and severe grades of hyperplasia. Cases of the latter, however, are rare and in the majority of them there is not the slightest resemblance to cancerous tissue. Cullen [76] was emphatic on this point. Schroeder [21b] stated that the merging of the condition into malignancy

75. The Geo. P. Pilling & Son Co., Philadelphia.

76. Cullen, Thomas: Canad. M. A. J. **19**:411, 1928.

had never been observed. Novak [22g] was convinced that there is no predisposition to cancer. Hintze,[77] in a clinical follow up of twenty-four cases of hyperplasia, found no development of carcinoma. Mack [65] considered that there is no tendency to the development of carcinoma. Taylor [73] studied this point with particular care and stated:

> Whether from a practical standpoint hyperplasia is to be regarded as precancerous and treated as such remains an open question. The relative frequency of hyperplasia undoubtedly indicates that the individual patient with the disease is reasonably safe, nevertheless it appears that when hyperplasia is at all marked, the possibility of a predisposition to the development of cancer should be considered and the case regarded with the same degree of suspicion now bestowed upon the diffuse forms of hyperplasia of the breast epithelium. In patients of the menopause age and older an adequate dose of radium is particularly indicated, certainly as the most efficient method of controlling bleeding, possibly as a prophylactic measure against the development of cancer.

Up to the present time we have noticed no evidence of hyperplasia developing into cancer in our cases. It is undoubtedly a rare occurrence and should have been noted more frequently if it is of causal significance.

Hyperplasia may occur at any time in life. It is decidedly more common at or near the menopause. Fluhmann [23b] found that 50 per cent of his patients were over 35 years of age. Schroeder [21d] gave the following data in regard to the age of occurrence: from 8 to 9 per cent of the patients were from 16 to 20 years of age; from 8 to 9 per cent were from 20 to 37; from 82 to 84 per cent were 37 and over. The greatest frequency was between 41 and 50. Many other authors gave somewhat similar figures. In Fluhmann's [23c] series of seventy-five patients, 53 had had full-term pregnancies preceding the onset of the condition, while fourteen were nulligravidae. Eight had had repeated abortions and never carried a baby to term. In two cases pregnancy occurred after a curettage had demonstrated hyperplasia. Vaginal bleeding is the chief symptom. It is often continuous, and patients are prone to present themselves for treatment during the spells of bleeding. In twenty-six of Shaw's [27] fifty-three cases there was a preceding history of amenorrhea, and most of the other authors noted the occurrence of the disease after a period of amenorrhea. Preceding the onset of continuous bleeding there may have been a long period in which menstrual irregularities and profuse periods were noted. In other cases the periods have been absolutely normal. The bleeding varies in intensity; sometimes the flow is moderate; in other cases it is excessive and frequently alarming. The presence of clots is often noted. During the time between periods of bleeding there is no intermenstrual discharge, unless the patient previously had some condition, such as gonorrhea, producing an intermenstrual discharge. A well developed secondary anemia is

77. Hintze, O.: Zentralbl. f. Gynäk. **53**:2396, 1929.

present in almost all the severe cases. The hemoglobin is frequently below 40 and may be as low as 25 per cent. As a result of the anemia, dyspnea, palpitation, faintness and headache are noted. Cramping or colicky pain accompanying the bleeding is generally absent. It may be present during the passage of clots. A unilateral or bilateral sense of vague pelvic discomfort is sometimes noted in conjunction with ovarian cysts. The discomforts of an associated prolapse are augmented during the bleeding spells.

Any general debilitating condition may precede the onset of the disease. Pregnancy, the removal of ovarian tissue and pelvic inflammatory disease are often noted in the previous history. Several of our cases have occurred following abortions. Constitutional habitus does not seem to play an especially prominent rôle, although one is struck by the frequent occurrence of the disease in obese women with hairy faces.

On pelvic examination the cervix may be slightly bluish; it is generally soft and patulous during the bleeding. The body of the uterus varies in consistency, being sometimes hard and at other times doughy. Often it is symmetrically enlarged. A small cyst, rarely larger than one's fist, may be palpated in the adnexal region.

The condition must be differentiated from cancer, abortion, fibroid and unruptured ectopic pregnancies as well as from luteal polymenorrhea. The patients with cancer of the body of the uterus are usually older and have a foul serous or watery discharge between periods of bleeding. Postmenopausal bleeding is more frequent in cancer than in hyperplasia. Abortion is suspected on account of the preceding period of amenorrhea and the soft, open condition of the cervix. The age of the patient and the absence of cramping pain speak against abortion. A submucous fibroid can produce many of the symptoms of hyperplasia. Dysmenorrhea, the presence of a hard cervix and the tendency to maintain a cyclic character are suggestive. A difficult problem is often raised by the preceding amenorrhea, adnexal mass and slight bleeding suggesting an unruptured ectopic pregnancy in the younger patients. Shaw [27] held that the disease can be diagnosed with a moderate degree of ease if an accurate menstrual history is available. Our experience substantiates the view that a careful history and physical examination will often lead to a correct diagnosis. While the percentage of error is small, the results of error are serious, and we advocate a study of the endometrium before a final diagnosis is arrived at. Curettage is the general method of obtaining tissue. The possibility of overlooking a circumscribed cancer is theoretically less with curettage than with our biopsy method. However, the latter method is so easy and convenient, and the possibility of a circumscribed cancer is so small that we have been

using the method more and more. A single insertion of the instrument can obtain two pieces of tissue at various points in the cavity of the uterus, and, if one elects, the procedure can be repeated many times. It is therefore possible to obtain almost as many different samples of tissue as can be obtained by the use of the curet. Since this method does not require hospitalization and can be carried out on ambulatory patients there is no valid excuse for not confirming the diagnosis by an examination of the tissue.

The prognosis of the disease as regards life is good, although fatal cases have been reported by Plaut [78] and Munzescheimer.[79] Some patients, for no apparent reason, spontaneously recover, while others continue to bleed and require treatment. Pregnancy may occur after a spontaneous recovery, as mentioned by Fluhmann.[23b] In other instances a cessation of the bleeding is followed by long periods of amenorrhea which are permanent in the older age groups.

The disease is particularly amenable to treatment, and cures can be obtained by the use of hormones, radiotherapy, curettage and hysterectomy. Recent experiences with the so-called anterior pituitary hormone obtained from the urine of pregnant women have been most encouraging. Owing to the similarity of action between it and substance from the anterior lobe it was called prolan by its discoverers, Zondek and Aschheim.[80] Collip [81] found a somewhat similar substance in the placenta. The experiments of Reichert, Pencharz, Simpson, Meyer and Evans [82] and of Hill and Parkes [83] have cast some doubt on the hypophyseal origin of the substance, and it is not improbable that it acts by stimulating the hypophysis, which in turn stimulates the ovary. Good results could be explained as due to the rise in estrogenic substance which would cause a regeneration of the endometrium and a cessation of the bleeding. As previously mentioned, there is a good deal of evidence pointing to a decrease of the estrogenic substance in the blood as being responsible for the degenerative changes resulting in bleeding. Owing to the excessive luteinization of the ovaries of experimental animals the substance came to be known generally as the anterior pituitary luteinizing substance, and as a result there was a tendency to attribute good results in human beings to luteinization. In the discussion of Novak and Hurd's [69] article on the results obtained with the so-called

78. Plaut, M.: München. med. Wchnschr. **76**:112, 1929.

79. Munzescheimer, J.: Zentralbl. f. Gynäk. **54**:2953, 1930.

80. Aschheim, S., and Zondek, B.: Klin. Wchnschr. **7**:1407, 1928. Zondek, B.: Klin. Wchnschr. **8**:157, 1929.

81. Collip, J. B.: Endocrinology **15**:315, 1931.

82. Reichert, F. L.; Pencharz, R. I.; Simpson, M.; Meyer, K., and Evans, H. M.: Am. J. Physiol. **100**:157, 1932.

83. Hill, M., and Parkes, A. S.: J. Physiol. **71**:40, 1931.

luteinizing hormone from the anterior pituitary lobe, Geist [84] reported a series of twenty-two women who were treated with this material preoperatively and whose ovaries showed no excessive luteinization. In closing the discussion Novak [85] expressed the belief that the effect of bleeding is due not to the histologic effect but to an effect on some unknown factor causing the bleeding. Klingler and Burch [86] reported a case in which serial biopsies were made. They concluded that the extract may exercise its immediate effect without producing progestational proliferation. We have found it most efficacious if given in doses of 100 rat units daily at the time the patient is seen, if bleeding is present; if there is no bleeding, the same amount is given, starting on the first day of the period and continuing until it stops. Usually the bleeding will stop within a reasonable time following this treatment. The extracts are somewhat unstable, and fresh preparations should be obtained if possible. Scattered reports from abroad indicate good results from commercial extracts of corpus luteum. As yet these extracts are not available in this country. Novak has repeatedly called attention to the rationale of this procedure. Favorable results have also been reported from parathyroid extract-Collip and from insulin and thyroid extracts. In cases in which hormone therapy fails one must turn to the older forms of treatment. Radium and roentgen rays find their greatest field of usefulness near the menopause, and the results are brilliant. By the use of the biopsy method and roentgen rays, hospitalization can be avoided in suitable cases. In very young patients curettage gives relief from the bleeding and furnishes an opportunity to correct any constitutional disturbance which may have been present. It should be repeated several times before a more radical form of treatment is decided on. Some years ago Dr. R. S. Hill,[87] of Montgomery, Ala., advocated injections of a solution of formaldehyde into the cavity of the uterus. He failed to publish his method, and it is therefore relatively unknown. Ochsner and Sullivan [88] have modified Hill's method and have stated:

> Instead of injecting the full strength formalin into the cavity, we pack the cavity for two minutes with plain sterile gauze saturated with full strength formalin. This procedure is, we believe, at least as effective as radiation and has none of its objections.

We have had no experience with the method of treatment suggested by Hill, but we intend to try it. After the failure of conservative methods, hysterectomy with retention of one or both ovaries is preferable to large doses of roentgen rays or radium in patients of the age group between puberty and the menopause.

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84. Geist, S. H.: Am. J. Obst. & Gynec. **22**:935, 1931.
85. Novak, Emil: Am. J. Obst. & Gynec. **22**:935, 1931.
86. Klingler, H. H., and Burch, J. C.: Am. J. Obst. & Gynec. **26**:17, 1933.
87. Hill, R. S.: Personal communication to the author.
88. Ochsner, E. H., and Sullivan, J. Kenneth: Illinois M. J. **61**:316, 1932.

Notes and News

University News, Promotions, Resignations, Appointments, etc.—Appointments and changes in title have been made at the University and Bellevue Hospital Medical College in New York as follows: Douglas Symmers, professor of pathology and director of the pathologic laboratory; Irving Graef, assistant professor of pathology; J. A. Klosterman, associate professor of bacteriology; Maurice Brodie, assistant professor of bacteriology.

John R. Schenken has been appointed instructor in pathology in Georgetown University, Washington, D. C.

At the University of Witwatersrand, Johannesburg, South Africa, a professorship in forensic medicine has been established in cooperation with the government in order to secure better medicolegal service. The professor of forensic medicine will act also as the chief district surgeon or medical examiner for Johannesburg.

Appointments by Medical Fellowship Board.—At the meeting of the Medical Fellowship Board of the National Research Council, March 31, 1934, the following appointments were made: Ralph W. Barris, neurology; Harold Blumberg, biochemistry; Dean A. Clark, neurology; Jack M. Curtis, biochemistry; Henry S. Dunning, pathology; Harry B. Friedgood, physiology; Benjamin F. Miller, medicine; Myron Prinzmetal, cardiovascular physiology and pathology; Robert Tennant, pathology.

Society News.—The officers of the American Society for Experimental Pathology for 1934-1935 are: S. B. Wolbach, president; Oskar Klotz, vice-president; Shields Warren, secretary-treasurer.

E. L. Opie has been elected president of the Society for Experimental Biology and Medicine; P. E. Smith, vice-president; A. J. Goldforb, secretary-treasurer.

The new officers of the American Society for the Control of Cancer are: Burton T. Simpson, president; Henry K. Pancoast, vice-president; J. M. Wainwright, secretary; Calvert Brewer, treasurer; James Ewing, chairman of the board of directors.

The recently elected officers of the American Association for Cancer Research are: Millard C. Marsh, president; E. T. Bell, vice-president; William H. Woglom, 1145 Amsterdam Avenue, New York, secretary-treasurer.

The newly elected officers of the American Association of Immunologists are: Francis G. Blake, president; A. F. Coca, secretary and treasurer. The next meeting will be held at Cornell University Medical College, New York, on April 17 and 18, 1935.

At its recent meeting in Toronto the American and Canadian Section of the International Association of Medical Museums elected William Boyd president, Virgil H. Cornell vice-president and Maude E. Abbott, McGill University, Montreal, secretary-treasurer.

T. M. Rivers and J. H. Northrop, members of the Rockefeller Institute for Medical Research, have been elected to membership in the National Academy of Sciences.

American Type Culture Collection.—In 1911 a Bacteriological Collection and Bureau for the Distribution of Bacterial Cultures was established at the American Museum of Natural History in New York City with C. E. A. Winslow as curator. Its catalog, issued in 1912, contained 350 species. In 1922 this collection was placed in the care of the Army Medical Museum in Washington. In 1925, through the urging of the Division of Medical Sciences of the National Research Council, the General Education Board made an appropriation of $24,000 for the maintenance of the collection, to be paid over a period of five years. At this time 175 cultures, which represented what remained of the collection, were

transferred to Chicago as the nucleus of the American Type Culture Collection. The collection was placed in the care of the John McCormick Institute for Infectious Diseases, under the direction of a committee representing the Society of American Bacteriologists, the American Phyto-Pathological Society, the American Zoological Society and the American Association of Pathologists and Bacteriologists. The expense of maintaining and developing the collection has been provided by the grant of $24,000 from the General Education Board covering five years, a grant of $10,000 made in 1930 by the Rockefeller Foundation, an annual contribution of $400 from the Society of American Bacteriologists, a few contributions from commercial sources and the income from the sale of cultures. At first $1 was charged for cultures, but in 1931, when the support from the General Education Board terminated, the price was raised to $2 in order to cover expenses. From 1925 to 1933, 36,294 cultures were supplied to teaching institutions and others. The collection in Chicago now contains about 1,300 cultures. The preservation of the collection on the present scale is dependent almost entirely on the income from the sale of cultures. General support of the collection is earnestly requested. Those who describe new species are urged to deposit them with the collection. The address of the collection is 629 South Wood Street, Chicago.

Doctor of Medical Science.—The degree of Doctor of Medical Science has been authorized for graduate study by Columbia University on the ground that such a degree is needed to identify specially trained physicians. Three years' training after internship with original graduate medical work will be required of candidates for this new degree.

Obituaries

WILLIAM HENRY WELCH
1850-1934

The death of Dr. Welch on April 30, after a long though relatively painless illness that confined him to the hospital for fourteen months, leaves medicine in America deprived of one who was perhaps its greatest figure. No other person has contributed so much toward the development of medical education with the introduction of a new attitude toward medicine. His work in pathology and bacteriology was followed by a broader new conception of the organization of public health control and the establishment of a new school of hygiene and public health. And, as though this were not enough for one man, in his later years he aroused an intense interest in the history of medicine and founded the present institute devoted to that subject. But these three lines of activity which, as others have said, represent three periods in his career, are after all of less significance to this country and to the world in general than the extraordinary influence of his personality and his recognized wisdom, which made him sought out by all great foundations and governmental bodies for his advice in their undertakings. He was president at one time or other of most of the prominent scientific and medical associations and of the boards of scientific direction of such centers of research as the Rockefeller Institute, and at home he was the constant ideal last source of counsel and wise decision. In problems of research or any new plan, the question was always, "What will Dr. Welch think of it?"

Dr. Welch was born in Norfolk, Conn., on April 8, 1850, the son of an able and gifted physician, Dr. William Wickham Welch. After graduating at Yale and later in medicine at the College of Physicians and Surgeons of Columbia, he was an intern at Bellevue Hospital. In 1876, he went to Europe, where he worked in histology with Waldeyer and in chemistry with Hoppe Seyler at Strasbourg, and later with Wagner at Leipzig, and with Ludwig. Ludwig advised him to go to Cohnheim in Breslau, and, after a particularly stimulating semester there, where he completed his study of pulmonary edema, he visited Klebs in Prague and Chiari and others in Vienna.

When he came back to New York he was, after an interval, established in Bellevue Hospital Medical College, where he was given a laboratory and abundant material for the study of pathology. In Europe, he had been fortunate in being associated with such fellow students as Weigert, Ehrlich, Salomonsen and many others, and in New York he

had the fellowship of Prudden and the friendship of such men as Alonzo Clark, Delafield and the older Flint.

For six years he worked in New York, attracting eager students to his autopsy demonstrations and laboratory work. Then came his appointment to the professorship of pathology in the Johns Hopkins University in 1884. He spent that year in Europe, immersed in the new discoveries of Koch, Pasteur, Pettenkofer and others. As Tomlinson said, "Could Sinai itself impose its revelation on a climber, who was no Moses?" but though others in his time had gone in numbers to Europe to study, he brought back the spirit and impulse that stirred America to the enormous effort that has changed the whole of medicine.

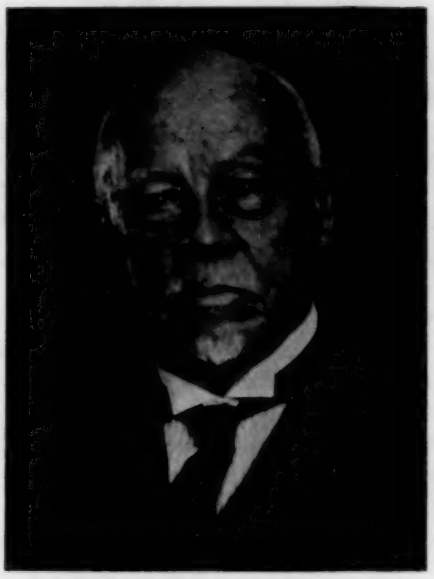
He returned in 1885 to Baltimore to begin work with a group of enthusiastic assistants, among whom were Councilman, Halsted, Mall, A. C. Abbott, Reed and Nuttall. The years until the opening of the medical school in 1893 were most productive, and Dr. Welch to the last loved to recall "that little group" with whom he plunged into the new bacteriology and immunity. Flexner arrived just before the medical school opened and remained until 1899, during which time he was much associated with Dr. Welch in studies of diphtheria and other subjects.

The influence of Dr. Welch in the choice of the first faculty of the School of Medicine seems to have been paramount, and there can be no doubt of the happiness of that selection. Osler, Halsted, Kelly, Mall and Abel were there, and during those years there was always a feeling in the school that any troublesome problem could be referred to Dr. Welch, with confidence in the wisdom of his reply. His lectures on pathology were most stimulating and suggestive, and his whole attitude stirred his assistants to great effort.

In 1917 he resigned from the chair of pathology and devoted himself to the broad problems of public health, with the new School of Hygiene as his headquarters. During that time, as always, his advice was sought on all sides. With the completion of each new institution for medical research, it was hoped that he would give the opening address, and he gave many of these, which were always inspiring to the workers in those places. His association with the varied activities of the Rockefeller Foundation took him twice to China, especially in connection with the newly founded Peking Union Medical College, and on other trips to Europe he was the honored guest or speaker on many occasions. In 1926, he resigned from the directorship of the School of Hygiene in order to devote himself to the history of medicine, for which a new foundation was set up. He went to Europe and everywhere sought out, and, with profound knowledge, chose books for the new institute. While he was away the Welch Library, which was to house the Institute of the History of Medicine, was planned and built, and on his return it was

opened with suitable ceremony. The photograph shown here was taken on this occasion in October 1929. Dr. Welch became emeritus professor of the history of medicine in 1931.

His writings are characterized by a remarkable clearness of style and a really extraordinary wealth of knowledge of the literature. They are long and detailed, but make delightful reading. His was a mind open to every source of information, completely free from prejudice and judicial in type, so that he carefully weighed statements on one side or the other and expressed his opinion after this precise balancing of the evidence.



WILLIAM HENRY WELCH, M.D.
1850–1934

His most important contribution to the facts of medicine are perhaps his discovery of the gas bacillus and his studies in diphtheria, hog cholera and the structure of thrombi, but his splendid papers on thrombosis and embolism and on fever and other subjects are of lasting value. Then, too, his expression in various papers and addresses of his ideas concerning medical education, public health and the organization of institutes of research will always be treasured and studied by medical men and those responsible for medical advances in the future.

He was, as every one knows, a most lovable character, entirely free from any undue sense of his own importance, so that he was accessible to all and so friendly that probably much of his time was occupied by

constant visitors. His friends were innumerable, and he was often the generous host at dinner at the Maryland Club. In the early days he spent much time there with a small group, including Dr. Halsted, Major Venable and Mr. Hambleton, in spirited conversation in a small room which has ever since somehow retained the memory of those meetings. They were epicures, too, Dr. Welch perhaps the most discriminating of all, and there was some truth in the New York prophecy that in Baltimore he would become an epicurean judge of terrapin and madeira. Later, he was for many years until his death president of the University Club and spent much time in its excellent library.

His memory was phenomenal, and no last detail seemed ever to fade out, although he read constantly such works as the "Encyclopaedia Britannica" and the "Dictionary of National Biography." Nor were his own experiences through a long life any more evanescent, for he could at any time recount in detail the happenings of his school days or of a long past stay in Europe. His command of medical literature, whether relating to pathology or to the history of medicine, was remarkable, too, and he gave many astonishing revelations of it.

He was, of course, honored in many countries by their universities, which conferred degrees or medals or some other distinction. On the twenty-fifth anniversary of his doctorate, a great volume of papers was published in his honor, and on his eightieth birthday every country vied with America to do him honor. His face is perpetuated in the Sargent portrait and in other portraits, notably one by Corner; a bronze bust stands in the Welch Library, and there is a moving talking picture in which he is seen recounting the experiences of his life.

It was a very perfect life, of great significance to the world, and on the whole intensely interesting and happy for himself. There was nothing to regret at any point, and his intellect and wisdom and remarkable sympathetically controlling personality were expressed to the full.

The organization of education in medicine, public health and the history of medicine owes its origin and progress largely to Dr. Welch's efforts and wisdom, and, beside that, his personal influence has been felt through all these years as a compelling inspiration to his many students who have carried his ideas all over the world.

His death is an irreparable loss, but his memory will not fade and will continue forever its stirring influence transmitted by those who knew him.

WILLIAM G. MACCALLUM, M.D.

Abstracts from Current Literature

Pathologic Anatomy

ATRESIA OF THE TRICUSPID ORIFICE. GEORGE R. MURPHY and LEO F. BLEYER, Am. J. Dis. Child. **46**:350, 1933.

A case is reported with postmortem observations of an infant about 4 months old showing congenital atresia of the tricuspid orifice with an interventricular septal defect, a patent foramen ovale and a rudimentary right ventricle. In addition to the cardiac condition, there was diffuse bronchopneumonic solidification, with delayed resolution and beginning cyanosis and dyspnea. If one includes the case of Cathala and Tisserand, this case is about the fifteenth reported showing this anomaly of the heart.

AUTHORS' SUMMARY.

CONGENITAL ABSENCE OF GALLBLADDER AND EXTRAHEPATIC DUCTS. J. MONTGOMERY DEAVER, Am. J. Dis. Child. **46**:356, 1933.

A white girl presented no abnormality until 6 weeks of age, when there began to be noticeable icterus. The icterus varied in intensity from day to day; the stools were clay-colored, and the urine was dark. There was a tendency toward constipation, and the child did not gain normally in weight. Repeated examinations of the stools and urinalyses gave negative results for bile pigment. The icteric index was 60, and the fragility test gave normal results. The Wassermann and Kahn tests were negative. The child died at the age of 1 year and 12 days. At necropsy the gallbladder could not be found, and careful dissection failed to reveal evidence of extrahepatic ducts. Both macroscopically and microscopically the liver showed marked biliary cirrhosis, with proliferation of the intrahepatic ducts. The papilla of Vater was absent. The spleen showed passive congestion, fibrosis of the pulp and hemosiderin pigmentation.

RALPH FULLER.

FETAL ENDOMYOCARDITIS: INTRAUTERINE INFECTION AS THE CAUSE OF CONGENITAL CARDIAC ANOMALIES. SIDNEY FARBER and JOHN HUBBARD, Am. J. M. Sc. **186**:705, 1933.

Fetal endomyocarditis as one of the causes of congenital heart disease is discussed. A summary is given of ten cases recorded in the literature and of four cases observed by the authors. The patients were all free from congenital syphilis. In each of the fourteen cases there was gross as well as microscopic evidence of old infection. In view of the early death of each infant it appears that the infectious process must have occurred during intra-uterine life. The nature of the infection is uncertain.

FROM THE AUTHORS' SUMMARY.

STRUCTURE AND FUNCTION OF FILAMENTS PRODUCED BY LIVING RED CORPUSCLES. JOHN AUER, Am. J. M. Sc. **186**:776, 1933.

The living red corpuscle of the guinea-pig, rabbit and dog and of man in hanging-drop preparations produces from one to five almost colorless, tapering, elastic filaments varying in length from 5 to 75 microns. Filaments may apparently arise from platelets. The filaments may appear within a few minutes after a hanging drop is made and may be readily detectable for more than twenty-four hours. They are composed of twisted fibrils, which in turn are composed of separately invisible subfibrils. The filament, fibril and subfibril are not sticky. The filament is motile and rotates around its long axis to the right and to the left; when one direction predominates, this ultimately causes a shortening. The

filaments anchor themselves peripherally to other red corpuscles, blood shadows, platelets or the edge of the drop. Their shortening distorts and compresses the red corpuscles into various shapes and may produce a microcyte with dense hemoglobin content. The filament may tear peripherally and roll up into a ball, change into a chain of refractile beads or thicken into a refractile rod. All these changes are reversible. The beads and the filament are not doubly refractile; both may appear free in the serum and execute active movements. Single free beads resemble blood dust, but are more lively at first. The formation of filaments is decreased or abolished by sufficient amounts of sodium oxalate, hirudin and heparin, but the formation of filaments is more resistant to these substances than the formation of fibrin from plasma fibrinogen. These filaments are probably the agents that cause the deformation of cells in sickle cell anemia. No contraction or intrinsic movement of typical fibrin threads from plasma fibrinogen was ever seen.

AUTHOR'S SUMMARY.

CARDIAC WEIGHTS. VICTOR LEVINE and JAMES G. CARR, Arch. Int. Med. **52**:429, 1933.

Sixty-four human hearts were divided and weighed according to the method described by Herrmann. These included normal hearts, hearts from persons who had died of some form of wasting disease, hypertensive hearts, hearts from persons who had died of rheumatic disease and hearts from persons who had died of cardiovascular syphilis, with and without involvement of the aortic valves. In patients dying of wasting disease the weight of the heart decreases slightly less than that of the body in general. In patients with rheumatic deformity of the mitral valve alone the increase in the weight of the heart is due to an increase in the weight of the right ventricle and of the auricles. In large hearts of persons suffering from rheumatism or syphilis with regurgitation at the aortic valves, the entire heart hypertrophies, but the greatest increase is in the left ventricle. The assumption that the left ventricle alone shows definite hypertrophy in cases of syphilitic aortic regurgitation of some duration is not acceptable. In the production of cardiac hypertrophy mechanical factors are not solely effective. The figures for the large hearts of persons with syphilis show diffuse cardiac hypertrophy whether or not aortic regurgitation was present. The size of hypertensive hearts without valvular disease does not equal that of hearts in which long-standing valvular defects are found at the aortic orifice. In the hypertensive type, however, the proportionate increase in the size of the left ventricle is greater than in other groups. A comparison of our work with that of Herrmann shows that the left ventricular weight right ventricular weight quotient of man is greater than that of the dog. The total ventricular weight/body weight quotient is twice as great for the dog as for man. The customary method of determining the thickness of the ventricular walls at autopsy is apt to be misleading as to the presence of right ventricular hypertrophy, which may be overlooked. The results obtained by the method that we employed and those obtained by Lewis with his method are similar for normal hearts and hearts with syphilitic lesions; they are approximately alike for hearts with rheumatic valvular deformity. In hypertensive hearts and the hearts of persons suffering from nephritis the results obtained by the two methods do not agree.

AUTHORS' SUMMARY.

XANTHOMATOSIS AND THE CENTRAL NERVOUS SYSTEM (SCHÜLLER-CHRISTIAN SYNDROME). CHARLES DAVISON, Arch. Neurol. & Psychiat. **30**:75, 1933.

Davison reports the forty-ninth case of xanthomatosis, in a man, aged 29: osseous defects, especially of the cranium; falling out of teeth; diabetes insipidus, and an increase in total fat, but absence of exophthalmos. The cholesterol content of the blood was normal. The anatomic changes were mainly plaques in the white substance of the brain, cerebellum, pons, medulla and basal ganglions. They appeared as areas of demyelinization which also contained fat granule bodies filled

with lipoids and were associated with marked reactive glial phenomena—the formation of large cytoplasmic glia cells. Around the tuber cinereum and in the visceral organs were large deposits of lipoids. The ganglion cells were, as a rule, preserved, but were destroyed in the tuber cinereum, which was sclerosed and fibrosed. Davison like other investigators considers the condition a lipoid (cholesterol) disturbance which resembles other conditions of disturbances of lipoid metabolism—Gaucher's disease, Niemann-Pick's disease and amaurotic family idiocy.

G. B. HASSIN.

MEGALENCEPHALY WITH DIFFUSE GLIOBLASTOMATOSIS OF THE BRAIN STEM AND THE CEREBELLUM. ARTHUR WEIL, Arch. Neurol. & Psychiat. **30**:795, 1933.

Diffuse glioblastomatosis is regarded as a hyperplasia of glial elements throughout the brain. There may also be an increase in the size of the nerve elements.

A boy who appeared normal at birth had a large head. At the age of 6 years and 4 months he showed apathy and a staggering gait, morning vomiting, drooling of saliva, slurring speech, exaggerated reflexes and the Babinski sign. The condition grew progressively worse and death occurred following bronchopneumonia.

The weight of the brain was 1,856 Gm.; the number of ganglion cells was apparently reduced without increase in the number of glia nuclei; there was a mild vascular infiltration in the white substance. In the diencephalon and midbrain the glia nuclei were increased in number, while the pons, the medulla, the roots of the cranial nerves and the cerebellum were densely infiltrated by glia cells. The ganglion cells were preserved. The pons, medulla, midbrain and thalamus were increased in size, with glioblastomatosis, but the enlargement of the cerebral hemispheres and corpora striata could not be explained by this neoplastic process. The frontal cortex was increased in thickness 45 per cent and the temporal cortex 30 per cent, but the number of ganglion cells was not increased. The hypertrophy of the cortex and corpora striata was due to isolated hypertrophy of the neuroglia, while the glioblastomatosis was confined to the brain stem, cerebellum and upper part of the cervical spinal cord. Glioblastomatosis is a diffuse process which begins simultaneously in different regions of the central nervous system. It differs from diffuse gliosis, in which there is hyperplasia of adult normal glia cells.

G. B. HASSIN.

IMPACTION OF A NEURO-EPITHELIAL CYST IN THE THIRD VENTRICLE OF THE BRAIN. CARL O. RINDER and PAUL R. CANNON, Arch. Neurol. & Psychiat. **30**:880, 1933.

A cystic tumor of the third ventricle is described in a woman who complained of acute dimness of vision, severe headache, projectile vomiting and severe pain over the right eye and in the temporal region. A few hours later she became comatose and died. There was an almost complete occlusion of the third ventricle by a cyst attached by a stalk to the anterior margin of the right choroid plexus. The contents were gelatinous, and the wall had an outer fibrous coat and an inner layer of cuboid and columnar ciliated epithelial cells. Some of the latter contained blue or yellowish-brown granules. The authors prefer the term "neuro-epithelial cyst" to "colloid cyst."

G. B. HASSIN.

CONTRACTED KIDNEY DUE TO PYELONEPHRITIS. W. T. LONGCOPE and W. L. WINKENWERDER, Bull. Johns Hopkins Hosp. **53**:255, 1933.

Nine patients have recently come under observation, five of whom have died in uremia and have been examined at autopsy. Most of the patients were women, and the disease in each case was probably of long duration. The course in some cases was characterized by attacks of pyuria accompanied by pain in the lumbar region and sometimes by fever. In some patients the course was practically symptomless until uremia suddenly appeared. In five of the nine cases there was

hypertension, while in four the hypertension was combined with hemorrhagic retinitis and arteriosclerosis of the retinal vessels. In the cases of hypertension there was rarely edema unless cardiac failure occurred. In all the patients dry skin, progressive anemia and polyuria were present. There were no evidences of cystitis, except in one patient. Pyelograms showed irregularities of various types in the size and shape of the kidneys, pelvis and calices. The specific gravity of the urine was constantly low, and the amount of albumin was small. Casts were rarely present; red blood cells were scarce or absent, except in one patient with ulcers of the bladder. Evidence of impairment of renal function appeared sometimes years before death and occasionally progressed to a remarkable degree without serious symptoms. Death came in uremia. At autopsy the kidneys were reduced in size, extremely uneven, scarred and distorted and showed irregular, slightly dilated pelves, which presented varying degrees of inflammation. Microscopically, areas of inflammation or retracted scars running from the cortex replaced large portions of renal tissue. Between these areas the comparatively normal kidney tissue was irregularly disposed. There was no gross obstruction to the flow of urine. It is not clear whether the disease arises from bilateral hematogenous infection of the kidneys or from an ascending infection from the bladder. At the time of writing treatment was being directed toward obtaining adequate drainage of the pelvis of the kidney.

FROM THE AUTHORS' SUMMARY.

LYMPHOID TISSUE IN THE SUBSTANCE OF THE KIDNEY. J. W. S. BLACKLOCK, J. Path. & Bact. **37**:504, 1933.

Foci of lymphoid tissue containing perfectly formed lymph follicles with germ centers were present in the cortex and, to a less extent, in the medulla of a kidney which was the seat of multiple subacute abscesses and inflammatory infiltration following scarlet fever.

PATHOLOGIC HISTOLOGY OF THE OMENTUM. P. JEBEL, Beitr. z. path. Anat. u. z. allg. Path. **91**:441, 1933.

The occurrence of metastases of gastric carcinoma in the omentum and the possible relation of such metastases to lymphoid tissue led to a histologic examination of the omentum in eighty-four cases which came to necropsy in persons of various ages from childhood to old age. The perivascular cellular accumulations that form the milky patches of the omentum of the new-born infant and of lower animals were not seen. The lobules of fat on the surface and margin of the omentum are bounded by a fine fringe of connective tissue, by means of which the omentum becomes attached to surrounding structures when acutely inflamed. Lymphoid follicles are present in the gastrocolic ligament at its attachment to the greater curvature of the stomach, but none was found in the omentum itself. Although metastasis of tumors to the omentum by way of the blood stream is possible, metastasis occurs usually by implantation and not by retrograde lymphatic transport of tumor cells. Atrophy of the omentum in cachectic states is due to disappearance of fat; the connective tissue framework becomes relatively prominent and may form whitish patches. Chronic inflammation of the omentum is associated with the presence of fibroblasts, histiocytes, lymphocytes and plasma cells, but lymphoid follicles are not formed. Leukocytic infiltration in acute inflammation is due to emigration of leukocytes from the vessels of the omentum.

O. T. SCHULTZ.

RHINOSCLEROMA AT NECROPSY. W. NOWICKI, Beitr. z. path. Anat. u. z. allg. Path. **91**:457, 1933.

Although rhinoscleroma is a common disease in the portion of Poland in which Lemberg is situated, few persons with this disease are seen on the necropsy table, evidently because the disease is rarely the immediate cause of death or of a terminal

illness that leads to hospitalization. In Nowicki's institute at Lemberg 23 cases of rhinoscleroma were encountered at necropsy within thirty-six years in a total of 31,962 necropsies. The disease may be the cause of sudden death through asphyxia or through hemorrhage complicating tracheotomy. Nowicki included in his series 8 cases of this type from the local medicolegal institute. Males and females were equally affected. Most of the cases occurred in young persons; 5 occurred in the age period of from 11 to 20 years, and 17 in the decade of from 21 to 30 years. The process was not limited to any particular portion of the upper respiratory tract. The larynx was most often involved, but usually in association with the nose, trachea and primary bronchi. Four anatomic forms are described: nodose, tuberous, diffuse and cicatricial. The essential features of the 31 cases are presented in tabular form.

O. T. SCHULTZ.

INVOLVEMENT OF THE APPENDIX IN THE PRODROMAL STAGE OF MEASLES. W. FISCHER, Beitr. z. path. Anat. u. z. allg. Path. **91**:475, 1933.

This is another of the rare instances in which the diagnosis of acute appendicitis during the prodromal stage of measles furnished the pathologist an interesting specimen for histologic study. The lymphoid follicles contained numbers of the peculiar giant cells first described independently by Warthin and by Finkeldey as present in the tonsils in measles and by Finkeldey as present in the appendix. Fischer suggests the histologic examination of Koplik's spots [Davidsohn, I., and Mora, J. M.: Appendicitis in Measles, ARCH. PATH. **14**:757, 1932].

O. T. SCHULTZ.

REDUPLICATION OF THE RIGHT AURICLE OF THE HEART; UNUSUAL CHANGES IN THE PULMONIC ARTERIES ASSOCIATED WITH PATENT FORAMEN OVALE. H. GOMBERT, Beitr. z. path. Anat. u. z. allg. Path. **91**:483, 1933.

Reduplication of a cardiac atrium unassociated with other gross malformations of the heart is a rare anomaly. Gombert could collect only fifteen instances from the literature. In fourteen the left auricle was double; in only one other case was there reduplication of the right auricle similar to the condition described. Both cases occurred in adults, Gombert's patient being a woman, aged 42. The left auricle was enlarged, and its wall was hypertrophied. The right auricle appeared small externally. It consisted of two cavities, each the size of a walnut. The superior vena cava emptied into the middle auricle. The inferior vena cava opened into the lateral portion of the duplicated right auricle, but delivered most of its blood into the left auricle through a large foramen ovale. The two parts of the right auricle communicated with each other by a small opening through the septum that separated the two parts. The anomaly is ascribed to a failure of union of the primitive auricular septum. In another case, also in a woman, aged 42, an open foramen ovale and hypertrophied right side of the heart were associated with peculiar changes in the terminal branches of the pulmonic artery in the lungs. A proliferation of the endothelium at the point of division of the small arteries acted as a sort of valve. Beyond this point the vessel was tortuous and angioma-like. The condition is ascribed to the altered mechanics of the pulmonary circulation.

O. T. SCHULTZ.

REACTION OF SUBCUTANEOUS CONNECTIVE TISSUE TO INJECTED FINELY DIVIDED STONE DUST. E. BENECKE, Beitr. z. path. Anat. u. z. allg. Path. **91**:503, 1933.

For the experimental work reported finely divided stone dust was used. It contained 56 per cent silicic acid and 18 per cent iron oxide. More than 70 per cent of the particles were 5 microns or less in diameter. Rabbits, guinea-pigs and rats were used. A 20 per cent suspension of sterile dust was injected subcutaneously or intraperitoneally. The dose varied from 3 to 6 cc., depending on the species of animal and the route of injection. There were no changes in the tissues that could

be ascribed to the chemical activity of the injected material. The only reaction was the formation of a foreign body granuloma. In a third of the rats there was noted necrosis with softening of the centers of the subcutaneous nodules, similar to what occurs in silicotic nodules of the human lung. Intraperitoneal injection led to the formation of silicotic granuloma in the spleen and liver in two rats, similar to the change noted in these organs in some cases of human silicosis.

O. T. SCHULTZ.

ATHEROSCLEROSIS OF CEREBRAL ARTERIES. K. WOLKOFF, Beitr. z. path. Anat. u. z. allg. Path. **91**:515, 1933.

Wolkoff reports the results of a histologic study of normal and pathologic cerebral arteries in eighty-nine necropsies of persons ranging in age from 2 to 81 years. The pathologic study relates to atherosclerosis, which is compared with the same process in other arteries. Since the work was done in Anitschkow's institute, infiltration with lipoid is accepted as the primary process in atherosclerosis. This process in the cerebral arteries differs in none of its essential features from that in the aorta and the coronary arteries. Infiltration with lipoid occurs in previously normal vessels and is usually localized at the mouths of the larger arteries at the base of the brain or at the origin of their side branches or in the more convoluted portions of the vessels. At these points the intima is normally thicker than elsewhere. Marked atherosclerosis of the larger arteries was occasionally associated with diffuse infiltration of their smaller branches with lipoid. As compared with the aorta and coronary arteries minor differences were the later development of atherosclerosis in the cerebral arteries, the lesser degree of calcification and the slight evidence of regressive or reparative changes.

O. T. SCHULTZ.

CHANGES IN THE BLOOD DUE TO XYLENE. MARIA FÄRBER, Beitr. z. path. Anat. u. z. allg. Path. **91**:554, 1933.

This is a repetition of some earlier work of Woronow, who claimed that derivatives of benzene with a methyl grouping cause changes in the blood of rabbits similar to those of leukemia. In Färber's experiments, 1.5 cc. of xylene in an equal quantity of olive oil was injected subcutaneously into rabbits twice daily. Changes similar to those noted by Woronow resulted. These were hyperleukocytosis, a shift to the left in the leukocytic formula, the appearance of monocytes and of degenerated and young cells of the granulocytic series and hyperplasia of the bone marrow. Färber found the hyperleukocytosis to be transient. Since this change and the shift to the left did not occur when rabbits were subjected to inhalation of xylene, she concludes that these alterations were the result of the local irritating and inflammatory action of the injected xylene. The degenerative changes in the leukocytes were the result of the toxic action of xylene; they occurred after both the injection and the inhalation of the substance. They are not specific for the methyl grouping of the compound, and the altered blood picture cannot be homologized with that of leukemia.

O. T. SCHULTZ.

INFLUENCE OF CEREBRAL DEVELOPMENT ON THE FACIAL SKELETON. E. HAMMER, Beitr. z. path. Anat. u. z. allg. Path. **91**:570, 1933.

Conclusions relative to the influence of development of the brain on the skeleton of the face are drawn from a study of fetal anomalies in which cerebral development was defective. The anomalies studied were divided into two main groups, holocrania and hemicrania. The former was subdivided into four groups of craniorachischisis totalis, with varying degrees of development of the brain. The cases of hemicrania were subdivided into those with and those without closure of the posterior arch of the foramen magnum and with varying degrees of cerebral development. The skeleton of the base of the skull and of the face was found

to have been laid down completely and therefore is initiated independently of the early development of the neural tube. But the further development of the base of the skull is directly influenced by the growth of the brain. Flattening of the primitive occipital bone, resulting from defective development of the brain and failure of closure of the cranial vault, affects the growth of the base of the skull and of the skeleton of the face. The effect on the latter is manifested chiefly in prognathism, abnormal width and height of the nose, malformation of the maxilla and shallowness of the orbits. The effect of congenital hydrocephalus, in which there is excessive action of those factors dependent on the size of the brain and the cranial vault, is contrasted with the effects of defective cerebral and cranial development.

O. T. SCHULTZ.

LOCALIZATION OF RHEUMATIC LESIONS IN THE HEART. M. M. LIEBER, Beitr. z. path. Anat. u. z. allg. Path. **91**:594, 1933.

Detailed histologic examination of the heart in five cases of active rheumatic infection confirmed the findings of others of the frequent localization of the lesions not only in the valvular tissues but in the coronary arteries, the root of the aorta and pulmonary artery, and the auricular endocardium, especially that of the left ventricle. The lesions were granulomatous and were histologically specific, as determined by control examinations of nonrheumatic hearts. Thrombotic deposit on the surface of the endocardial lesions is a secondary phenomenon, many endocardial lesions being devoid of such a deposit.

O. T. SCHULTZ.

THE MENSTRUAL CYCLE AND THE LIPOID CONTENT OF THE UTERINE MUCOUS MEMBRANE. INGEBORG GOHLISCH, Monatschr. f. Geburtsh. u. Gynäk. **94**:223, 1933.

One hundred specimens of uterine mucous membrane were examined for lipoids. Of these, twenty-two were taken in the interval between menstrual periods, seventeen at the beginning of the premenstrual period, thirty-five during the premenstrual period, four during the menstrual period and three during the decidual period. There were seventeen with cystic glandular hyperplasia, one with adenocarcinoma, and one showing polyp. Lipoid was demonstrated in the glandular epithelium in 20 per cent of the cases, chiefly in the premenstrual and menstrual phases. Rich amounts of lipoid were found in the glandular lumen in 50 per cent of the cases during the stage of recovery. There was diffuse distribution of droplets of fat in the stroma, especially during the premenstrual phase. These observations agree with those of Ascheim, who found lipoids chiefly in the premenstrual phase.

JACOB KLEIN.

RELATION OF FATTY CHANGE OF THE AORTIC WALL TO ARTERIOSCLEROSIS. D. GÖRÖG, Virchows Arch. f. path. Anat. **287**:602, 1933.

Study of seventy-three aortas convinced Görög that the first anatomic lesion of aortic arteriosclerosis consists of a small, circumscribed area of fatty degeneration of the inner layer of the elastica. This finding seems to support the assumption that arteriosclerosis is due to an increased functional demand on the wall of the vessel. While the normal wall is capable of meeting the increased functional demand, this ability becomes impaired by persistently increased demand due to poisons, metabolic products or bacteria and to constitutional, congenital or familial factors.

W. SAPHIR.

MALFORMATION OF THE BASILAR BONE ASSOCIATED WITH OSSEOUS UNION OF THE ATLAS AND SKULL. P. SINZ, Virchows Arch. f. path. Anat. **287**:641, 1933.

A man, aged 27, died with symptoms of cerebellar tumor. Necropsy revealed a peculiar hypoplastic malformation of the basilar bone, with protrusion of the bone into the cranial cavity. The protrusion and the osseous union of the atlas

with the skull had led to displacement and narrowing of the foramen magnum, with consequent obstruction of the circulation of the cerebrospinal fluid and internal hydrocephalus. Sinz considers a primary disturbance in the development of the basilar bone the most likely cause of this unusual condition. W. SAPHIR.

INTESTINAL RHINOSCLEROMA. W. ROTTER and A. PEÑA CHAVARRÍA, Virchows Arch. f. path. Anat. **289**:345, 1933.

Involvement of the alimentary tract in rhinoscleroma has not been hitherto described. In a case of the disease which came to necropsy in Costa Rica the mucosa of the cecum and ascending colon from the ileocecal valve to the hepatic flexure was studded with nodular elevations. The nodules were composed of granulation tissue that contained Mikulicz' cells and was histologically identical with the tissue of the nasal and upper respiratory tract lesions of rhinoscleroma. From their experience with this disease the authors have found that the number of Mikulicz' cells may vary greatly. The cells are most numerous in the recent and most acute lesions. Sometimes the histologic diagnosis must be based on the presence of hyaline cells. When the histologic changes are not characteristic, the diagnosis must depend on the isolation of the specific encapsulated bacillus.

O. T. SCHULTZ.

PRIAPISM IN A CASE OF SEPSIS. S. SCHEIDEGGER, Virchows Arch. f. path. Anat. **289**:378, 1933.

A youth, aged 17, fell astride a timber on which he was working. He was able to continue his work after the accident. The next day he complained of severe sore throat. On the fifth day he was admitted to a hospital with a necrotizing tonsillitis, swelling and discoloration of the perineum and erection and edema of the penis. The priapism, which persisted after death, was due to thrombosis of the corpora cavernosa and of the pelvic veins. The priapism is ascribed to a combination of thrombosis due to the accident and sepsis due to the tonsillar infection.

O. T. SCHULTZ.

LYMPHOGRANULOMATOSIS OF THE VERTEBRAL COLUMN. E. WEGEMER, Virchows Arch. f. path. Anat. **289**:386, 1933.

A man, aged 31, died after a twelve year course of the disease. Although the bodies of the vertebrae had been greatly rarefied, their shape had not been much altered, because of the replacement of bone by dense fibrous tissue. The latter process was the result of fibrosclerosis of the lymphogranulomatous tissue that had invaded the vertebrae. The condition was not, as others have maintained, osteosclerosis but fibrosis of the specific granulation tissue. O. T. SCHULTZ.

CONGENITAL LOCALIZED OSTEOMYELITIS OF THE SKULL. W. LADEWIG, Virchows Arch. f. path. Anat. **289**:395, 1933.

A child born five weeks prematurely died nineteen hours after a normal delivery. At birth a tumor-like elevation of the scalp was noted in the left parietal region. Necropsy showed this to be an area of localized osteomyelitis of the parietal bone, with abscess. The inflammatory process had extended to the scalp and to the dura, where it was productive. There had been considerable new formation of bone. Diplococci could be seen in sections of the lesion. The process is held to have been the result of transplacental hematogenous infection. No history of infection of the mother during her pregnancy could be obtained.

O. T. SCHULTZ.

CHANGES IN THE HEART IN HYPERTHYROIDISM. A. DE CHÂTEL and W. MOLNÁR, Virchows Arch. f. path. Anat. **289**:557, 1933.

The hearts of seventeen patients who died of hyperthyroidism were subjected to histologic examination. The only changes noted were moderate hypertrophy, an increase in intracellular pigment, the presence of a few wandering cells with pigment and a diffuse slight increase in connective tissue. These changes were due to the increased functional activity of the cardiac muscle, followed by decreased activity and regression. Focal necrosis and inflammation, which has been described as toxic myocarditis due to hyperthyroidism, was not encountered.

O. T. SCHULTZ.

STUDY OF VASCULAR ANOMALIES BY MEANS OF INJECTION AND ROENTGENOGRAPHY. A. HINTZE, Virchows Arch. f. path. Anat. **289**:705, 1933.

Reproductions of seven excellent roentgenograms support Hintze's thesis of the value of contrast injection and roentgenography in the study of vascular anomalies. The method is the subject of a more or less general discussion. Three cases are described illustrating the differences between the vascular anomalies of congenital malformations and benign tumors, in which the variant vascular tree is looked on as physiologic and harmonic, and the abnormalities of the circulatory system in the presence of malignant tumors.

O. T. SCHULTZ.

SYMMETRICAL CORTICAL NECROSIS OF THE KIDNEYS. E. VON ZALKA, Virchows Arch. f. path. Anat. **290**:53, 1933.

Von Zalka found thirty-seven cases of symmetrical cortical necrosis of the kidneys recorded in the literature. Thirty-one of these were associated with pregnancy. He discusses the previous histologic findings in relation to two cases reported by himself, one in a girl, aged 13 years, and one in a man, 64 years old. In the child the renal involvement followed an attack of acute tonsillitis; in the man no history of antecedent illness could be obtained. Von Zalka agrees with the majority of other investigators that the necrosis is the result of thrombosis which occurs chiefly in the interlobular arteries and in the afferent and efferent arterioles of the glomeruli. He believes the thrombosis to be due to toxic injury of the endothelium.

O. T. SCHULTZ.

MASSIVE ANEMIC NECROSIS OF THE LUNG IN PNEUMONIA. M. REINISCH, Virchows Arch. f. path. Anat. **290**:75, 1933.

Reinisch reviews the small number of reported cases of pneumonia that terminated in massive anemic necrosis of the inflamed lung. The case which he reports was that of a 5 year old boy, who became suddenly ill the middle of January with a characteristic attack of pneumonia. The temperature returned to normal on the tenth day, but rose again two days later. Admission to the hospital occurred on February 12, at which time there was flatness on percussion of the lower part of the thorax on the left posteriorly; breath sounds were absent in this region. On the next day half a liter of purulent exudate was removed from the left side of the chest by thoracotomy. Death occurred on February 21. Necropsy revealed two relatively large, sharply defined areas of ischemic necrosis in the organizing upper lobe on the left. Reinisch divides the recorded cases of the condition into three groups. In the first two the essential factor is arterial thrombosis. The anemic character of the infarct is due to the inflamed state of the lung, which prevents the backflow of blood through the collateral capillaries. In the first group the lesion contains no bacteria, and the condition is termed aputrid anemic necrosis. In the second group bacteria are present; the condition is called septic anemic necrosis. In the third group, in which Reinisch places his own case, the essential factor is bacterial activity. Bacterial action causes thrombosis and necrosis; this group is called septic necrosis. The justification for making a distinction between the second and third groups does not appear well founded.

O. T. SCHULTZ.

LYMPHOGRANULOMATOSIS OF THE STOMACH AND XANTHOMATOSIS OF THE MESENTERY. W. BAUMGARTNER, Virchows Arch. f. path. Anat. **290**:97, 1933.

The reported case of Hodgkin's disease is one of the rare ones in which the lymphogranulomatous process is limited to the stomach. No other organs or lymph nodes were involved. In the wall of the jejunum and stomach and in the root of the mesentery were yellow nodules. These were composed of large foam cells filled with lipoid. Baumgartner does not believe that the xanthomatosis was part of the lymphogranulomatous process.

O. T. SCHULTZ.

Microbiology and Parasitology

RHEUMATIC MANIFESTATIONS IN SUBACUTE BACTERIAL ENDOCARDITIS IN CHILDREN. O. SAPHIR and S. A. WILE, Am. Heart J. **9**:29, 1933.

A study of ten cases of subacute bacterial endocarditis, eight in children and twelve in young adolescents who had been under observation since childhood, is reported. The histories revealed evidence of a preceding rheumatic infection in every instance. All hearts showed healed endocarditis, subacute bacterial endocarditis and Aschoff bodies in the myocardium, in addition to other changes. The blood revealed pure cultures of Streptococcus viridans, and smears from the vegetations showed gram-positive cocci in chains. The relation between the rheumatic infection and the final subacute endocarditis is discussed. A concurrence of these two conditions, though not definitely excluded, seems unlikely. Although allergy is an attractive explanation of rheumatic fever and its relation to subacute endocarditis, evidence is brought forward which seems to speak against rheumatic fever being an allergic phenomenon and the assumption that both conditions are manifestations of the same disease, differing only in the immunologic response of the host. At present the weight of evidence seems to be that the only relationship between rheumatic fever and subacute endocarditis is that the injury due to a previous rheumatic infection predisposes the valve to a subsequent endocarditis. The conclusion is reached that the Aschoff body is a characteristic structure and a specific reaction caused by the unknown virus of rheumatic fever. The circumscribed cellular infiltrations produced experimentally in hypersensitive animals, though morphologically resembling Aschoff bodies, are in no way characteristic of them. The use of strict criteria for the identification of Aschoff bodies is urged. The fact that in a number of cases the rheumatic manifestations gradually merged into the picture of subacute bacterial endocarditis may account for recent Aschoff bodies in the myocardium of patients who died of subacute bacterial endocarditis.

FROM THE AUTHORS' SUMMARY.

THE PERMEABILITY OF THE KIDNEY TO BACTERIA. M. H. BOOK, Am. J. Path. **9**:569, 1933.

Staphylococcus aureus injected into the circulation of the normal rabbit did not appear in the urine until between eight and twelve hours later. Bacterium coli was absent from the urine even up to forty-eight hours after injection. Bacillus prodigiosus failed to reach the urine up to twenty-four hours after injection. The examination of ordinary paraffin sections to determine the exact site of a few individual bacteria is not entirely reliable. The method of incubating the kidney before fixation and staining not only facilitated greatly the finding of the bacteria, but permitted a more dependable analysis of the location of the organisms from which the colonies had developed. By means of such examination it was seen that the bacteria never reached the capsular space about the glomeruli or the lumens of the tubules in the first few hours after injection and hence were not excreted. The probability is that they did not get beyond the vascular system until they had damaged the walls of the latter.

AUTHOR'S SUMMARY AND CONCLUSIONS.

ACTINOBACILLOSIS OF MAN. D. C. BEAVER and L. THOMPSON, Am. J. Path. **9**:603, 1933.

Three cases of actinobacillosis in man are now well authenticated. The case concerned here offered the first opportunity for pathologic study of the lesions in a human being. The lesions were essentially similar to those that have been described in cattle except that they were much more widespread, and sulphur granules such as occur in the bovine lesions apparently did not occur. The lesions may be described as granulomatous abscesses severely affecting the lungs, liver and spleen. Lesions similar to those observed in man and cattle were produced in animals experimentally. Glanders and tularemia were considered in the differential diagnosis, but both seemed to be definitely ruled out by the bacteriologic and serologic investigations. The organism isolated reveals a close cultural and antigenic relation to Actinobacillus Lignièresi, and a more distant relation to Pfeifferella mallei and Bacillus Whitmori. Thompson has previously shown that A. Lignièresi of bovine and human origin, Pf. mallei and B. Whitmori are antigenically interrelated and has proposed that they be included in a common genus. This relationship, as far as the organism in the present case is concerned, is also confirmed from the pathologic point of view, for the lesions in man and the experimental lesions in animals were similar to those of glanders and also exhibited similarities to the lesions of bovine actinobacillosis. Although the organism under consideration revealed minor cultural differences and antigenic phenomena somewhat different from those of a typical strain of A. Lignièresi of bovine origin, nevertheless it seems justifiable to regard the organism as a variant of the usual bovine strain of A. Lignièresi. AUTHORS' SUMMARY.

THE PERSISTENCE OF TUBERCULOUS INFECTIONS. H. E. ROBERTSON, Am. J. Path. **9**:711, 1933.

Tuberculous infections may occur and pursue their entire course without demonstrable clinical phenomena, that is, without attracting the attention of the patient or a physician to their presence. Recognized tuberculous infections may subside and be regarded throughout remaining life as healed and still remain continuously active. Apparently healed tuberculous lesions may become clinically active after varying intervals. No form of physical examination can assure any person that he or she does not harbor the menace of active tuberculous infection. The safest rule for physicians and patients alike is to regard tuberculosis as possessing an ever present potentiality for becoming active. One can almost say: "Once infected, always infected." AUTHOR'S CONCLUSIONS.

TUBERCLE BACILLI IN THE BLOOD IN ADVANCED PULMONARY TUBERCULOSIS. H. J. CORPER and A. P. DAMEROW, Am. Rev. Tuberc. **28**:118, 1933.

Tubercle bacilli were not found in the blood of 120 patients with advanced and generalized tuberculosis. Each blood specimen was submitted to four methods of examination for tubercle bacilli, namely, inoculation in guinea-pigs and three different cultural methods. While control tests proved the efficacy of the cultural methods used for discerning small numbers of tubercle bacilli in human and animal blood, acetic acid, as recommended by Loewenstein, destroyed small numbers of tubercle bacilli while permitting saprophytic acid-fast bacilli to survive, thus vitiating the results obtained with this reagent. Over 200 smaller specimens obtained as a routine from patients in a sanatorium and examined by two cultural methods, the tissue substrate method and the sulphuric acid-crystal violet-potato-cylinder method, did not yield a single culture positive for tubercle bacilli. Of the 120 patients whose blood was examined, 2 yielded saprophytic acid-fast bacilli which were proved not to be pathogenic tubercle bacilli. Tubercle bacilli, when present in small numbers, grow well on a sulphuric acid-treated and sodium bicarbonate-neutralized or sodium hydroxide-neutralized blood residue or on inspissated defibrinated blood, making it appear that acid-treated or heat-treated

or sterilized blood pigments are not detrimental to the growth of tubercle bacilli. The macroscopic type of culture obtained on the blood medium differs from that seen on potato or that on egg, which also differ from each other. The congo red-potato flour-egg medium (Loewenstein) is a good one for human and bovine tubercle bacilli, but it is not better than a simple potato cylinder or inspissated egg-yolk medium. It appears that human or bovine tuberculobacteremias, in the sense that tubercle bacilli circulate in the blood for a fairly long time or that the bacilli multiply in the blood, are not borne out by these studies, although it is not intended to convey the impression that occasional embolic disseminations (showers) from disintegrating tuberculous foci do not occur or that there are not terminal periods in the course of the disease when showers of caseous products containing visible bacilli may make it possible to find them in the blood of man and experimental animals. Such a condition of tubercle bacilli in the blood is far from being the common event. Embolic showers, when they occur in man, are rapidly removed from the circulation, in the usual case of tuberculosis.

H. J. CORPER.

THE COCKROACH AS A POSSIBLE CARRIER OF TUBERCULOSIS. HENRY C. READ, JR., Am. Rev. Tuberc. **28**:267, 1933.

The cockroach may be considered a possible mechanical carrier of tuberculosis for the following reasons: 1. All smears of the intestinal tracts of cockroaches allowed to feed on infected sputum showed tubercle bacilli. 2. The organisms recovered from the intestinal tract were viable, for they produced lesions in guinea-pigs. 3. Microscopic sections did not show the bacilli to be present in the tissues, thus showing that they remain in the intestinal tract.

H. J. CORPER.

TUBERCULOSIS OF HUMAN ORIGIN IN AN AMAZON PARROT. W. R. HINSHAW, Am. Rev. Tuberc. **28**:273, 1933.

A case of tuberculosis in a male "Amazon parrot" (genus Amazona) is reported. There was a history of the parrot's being the pet of a patient with tuberculosis, and inoculations in animals indicated that the bird was suffering from the human type of the disease.

H. J. CORPER.

POLIOMYELITIS VIRUS. J. R. PAUL and J. D. TRASK, J. Exper. Med. **58**:513, 1933.

That qualitative differences exist between so-called human and passage strains of poliomyelitic virus has been established by the following observations: (*a*) The experimental disease induced by two human strains usually failed to protect monkeys against a subsequent infection by a passage strain, and in the few instances in which the reverse experiment could be made a similar lack of protection was observed. (*b*) In some human serums the neutralizing power for a human strain differed qualitatively from that for a passage strain. The length of time between the intracerebral inoculations of heterologous strains has been found to be an important factor bearing on the results of the reinoculation experiments reported. Within the intervals used, the greater the period between the original infection and the reinoculation with a heterologous strain the less was the degree of cross-immunity observed.

AUTHORS' SUMMARY.

THE CULTIVATION OF VACCINE VIRUS FOR JENNERIAN PROPHYLAXIS IN MAN. T. M. RIVERS and S. M. WARD, J. Exper. Med. **58**:635, 1933.

A dermal strain of vaccine virus has been subjected to 99 successive cultural passages. This procedure led to a diminution in the pathogenicity of the active agent for the rabbit. By repeated testicular passages in rabbits, however, the virus regained its pathogenicity for that host. New cultures were initiated with

the revived virus. A culture strain of virus that has been twice revived in this manner has remained fairly stable for the rabbit through 60 cultural passages, and it produces mild, yet effective vaccinal reactions in man. Virus in early cultures was not attenuated for man, but later cultures of the original strain and cultures of the second and third revived strains produced mild reactions without fever and discomfort to the patients. Intradermal vaccinations with the culture virus are safe and satisfactory. With the culture virus 118 infants and children have been inoculated, and in 100 of them a positive reaction occurred. The culture virus produced a refractory state to a standard dermal strain of calf lymph and vice versa. Culture virus stored in 50 per cent neutral glycerin at —10 C. or at + 3 C. maintained a considerable amount of its activity for at least one year. Desiccated culture virus sealed in tubes maintained some of its activity when stored at 37 C. for five weeks. Fresh cultures can be initiated without difficulty from desiccated virus or from virus that has been stored with or without glycerol.

AUTHORS' SUMMARY.

CULTIVATION OF PSEUDORABIES VIRUS. E. TRAUB, J. Exper. Med. **58**:663, 1933.

Pseudorabies virus has been cultivated in series in rabbit testicle, guinea-pig testicle and chick embryo medium, and its growth requirements have been studied. Intranuclear inclusions similar to those produced by pseudorabies virus in vivo have been found in cultures on rabbit testicle medium. The virus has not changed its pathogenic properties for rabbits, guinea-pigs or mice during the course of cultivation.

AUTHOR'S SUMMARY.

THE FORMATION OF GREEN PIGMENT FROM HAEMOGLOBIN BY THE PNEUMOCOCCUS. P. D. HART and A. B. ANDERSON, J. Path. & Bact. **37**:91, 1933.

An olive green precipitate was formed when small quantities of laked blood were incubated aerobically with broth cultures of the pneumococcus to which alkaline phosphate solutions had been added. This precipitate could be separated, washed and extracted with dilute alkali to give a green solution. Suitable conditions for the formation of the pigment, including the optimal range of p_H, are described. When the mixtures were incubated anaerobically, reduced hemoglobin was formed; on subsequent aerobic incubation, this was converted into the green pigment. Aerobic or anaerobic cultures allowed to autolyze in air with phosphate solutions rapidly lost their ability to produce green pigment from blood. Cultures autolyzed under anaerobic conditions remained active for longer periods. Sterile filtrates of unautolyzed anaerobic cultures were found to be inactive. Active filtrates were obtained from anaerobic cultures only after disintegration of the organisms. The activity of sterile filtrates was rapidly destroyed by aeration, by the addition of hydrogen dioxide or by heating to 55 C. Addition of a solution containing catalase to cultures or filtrates retarded the destruction of activity brought about by exposure to air. Suspensions of washed organisms in phosphate buffer were themselves unable to produce the green pigment from blood but could be activated by meat extract and other substances. Extracts prepared from such washed organisms were not activated in this manner. Crystalline oxyhemoglobin, methemoglobin and, to a less extent, carboxyhemoglobin could replace laked blood as a source of the green pigment. The green pigment has not yet been identified; its physical and chemical properties do not correspond with those of any of the common derivatives of hemoglobin. The nature of the enzyme system involved in the formation of the green pigment and its possible identity with the system described by Neill and Avery (1924) are discussed.

AUTHORS' SUMMARY.

A VIRUS DISEASE OF THE CANARY OF THE FOWL-POX GROUP. F. M. BURNET, J. Path. & Bact. **37**:107, 1933.

The disease of canaries described by Kikuth and Gollub is caused by a virus closely resembling certain strains of the virus of fowl pox. The main histologic features of the disease are: (*a*) a proliferation of the dermal epithelium with cyto-

plasmic inclusions; (*b*) an inflammatory response of predominantly mononuclear cells showing characteristic vacuolation of the cytoplasm, and (*c*) a massive accumulation in the infected lung of large mononuclear cells containing specific cytoplasmic inclusions.

The virus produces massive lesions when it is inoculated into the chorioallantoic membrane of the developing egg. An improved technic for this type of inoculation is described. By filtration and photomicrographic methods the diameter of the particles of the virus is estimated to be approximately 0.16 micron. The disease is uniformly fatal to canaries, and no success has been attained in attempts to immunize them with killed virus. The virus is pathogenic for sparrows, producing typical lesions. Only an insignificant lesion is produced in the fowl, but a more definite transmissible inflammatory condition is produced in the pigeon. In neither of these species are epithelial inclusions found. Of three strains of the virus of fowl pox tested, one ("Dalling") produced lesions in the canary similar to those produced by Kikuth's virus. The other two strains and a strain of the virus of pigeon pox have failed to induce specific lesions.

AUTHOR'S SUMMARY.

CELLULAR RESPONSE OF VITREOUS HUMOUR TO BACTERIA, BLOOD AND VITAL DYES. W. A. GRAY, J. Path. & Bact. **37**:137, 1933.

The first cells to respond to the presence of irritation in the vitreous are polymorphonuclear leukocytes. They are quickly followed by macrophages; the macrophages increase, in the later stages of the inflammation, as the polymorphonuclear leukocytes diminish. The cellular exudate is derived almost entirely from adjacent vascular structures, but occasionally there is a proliferation of periadventitial histiocytes at the optic disk. The area of the wound produced during the injection of the irritant is the first and for a time the principal source of supply of the emigrating cells, but sooner or later they are derived from the optic disk and the pars plana of the ciliary body. Micro-organisms introduced into the vitreous tend to spread rapidly to the anterior chamber, to the ciliary body, especially the pars plana, and to the optic disk, where they call forth an inflammatory reaction.

AUTHOR'S SUMMARY.

CLASSIFICATION OF DYSENTERY-COLI BACTERIOPHAGES. F. M. BURNET, J. Path. & Bact. **37**:179, 1933.

There are sharp distinctions among bacteriophages in regard to rate of photodynamic inactivation by methylthionine chloride, U. S. P. (methylene blue), ability to lyse in the presence of citrate and rate of inactivation by strong urea solutions. Phages falling in a single serologic group as previously defined are approximately uniform in their response to any of these tests. Strong urea solutions inactivate large particle phages with great rapidity and (with one exception) are much less active on small particle phages. Several acridine dyes can be used for photodynamic inactivation of suitable phages.

AUTHOR'S SUMMARY.

THE STABILITY OF THE MITIS, INTERMEDIATE AND GRAVIS TYPES OF B. DIPHTHERIAE. M. H. CHRISTISON, J. Path. & Bact. **37**:243, 1933.

The three main types of Bacillus diphtheriae undergo marked variation in structure of colony in vitro, particularly after growth in bouillon. Rough variants derived from the mitis strain would at sight be classified as gravis and derivatives of gravis colonies as mitis. Variation also occurs in the type of growth in bouillon and in the production of hemolysin. Changes in structure of colony are observed not only in strains obtained from Leeds, but also in those isolated in Edinburgh. These findings and the occasional isolation of "atypical" strains suggest that dissociation occurs in vivo as well as in vitro. Gravis strains ferment starch irrespective of the structure of the colony, whereas intermediate and mitis forms and their

variants fail to do so. It appears, therefore, that in identifying the gravis type the fermentation of starch is a more reliable criterion than the structure of the colony.

AUTHOR'S SUMMARY.

MECHANISM OF ANTHRAX INFECTION. A. BOQUET and A. SAENZ, Ann. Inst. Pasteur **50**:311, 1933.

Hemorrhagic or necrotic exudate was considered less significant than progressive bacteremia. Boquet and Saenz take exception to Besredka's statement that the skin exclusively is sensitive to anthrax organisms. Presumably owing to the greater activity of the wandering cells and histiocytes in the subcutaneous tissue the latter was demonstrated to be four or five times less receptive than the skin. Experiments with inhalation resulted in a fatal septicemia emanating from the pulmonary alveoli, as appears to occur in human infection. Intraperitoneal injections often resulted in aborted infections, but when infection occurred it appeared to be due to multiplication of the organisms in the liver and spleen rather than to accidental contamination of the skin. Organisms fed in massive doses were at times noted in the blood stream from two to eight hours later, but no infection resulted, owing to rapid phagocytosis in the liver, spleen and bone marrow.

FROM THE AUTHORS' CONCLUSIONS.

FILTRABLE ELEMENTS IN TUBERCULOSIS. M. C. NINNI, Ann. Inst. Pasteur **50**:504, 1933.

Ninni believes that the invisible filtrable granular elements secured from young cultures of the tubercle bacillus and from infected organs are living and are capable of multiplication in vivo and in vitro; that the lymphatic Calmette-Valtis type of tuberculosis, without tubercles, is characteristic of their presence; that they may give rise to typical organisms, but are not to be confused with variously suggested artefacts; that young cultures of these forms are toxic for nerve cells; that they may pass the intact placenta of pregnant females, possibly causing death of the fetus or progressive malnutrition of the new-born, or producing immunity, and that the ultravirus together with the Koch bacilli constitute the virus of tuberculosis, thus affording, according to the balance, the great variety of clinical forms encountered.

FROM THE AUTHOR'S CONCLUSIONS.

HUMAN TUBERCLE BACILLUS ON BILE MEDIUM FOR TWENTY-TWO YEARS. A. CALMETTE, C. GUÉRIN and L. NÈGRE, Ann. Inst. Pasteur **50**:599, 1933.

The original B C G strain of the tubercle bacillus was of bovine origin. A strain of human derivation and of medium virulence was secured in 1908 from Trudeau's laboratory at Saranac, N. Y. Beginning March 10, 1910, a series of 418 successive parallel transfers were made in an alkaline medium containing potato, ox bile and glycerin. The virulence for guinea-pigs and rabbits appeared to increase in both the human and the bovine strain at first, but weakened after the thirty-fifth transfer. By 1921 a dose equivalent to 1 mg. failed to affect these animals. The avirulence and the antigenic and immunizing properties of the human strain appeared to be equivalent to those of B C G. No substitutions in B C G vaccine were contemplated, but the stability of the parallel strain in a study of this type was considered significant.

M. S. MARSHALL.

PATHOGENESIS OF MENINGOCOCCIC MENINGITIS. P. ZDRODOWSKI, Ann. Inst. Pasteur **50**:651, 1933.

A fatal meningitis was produced in rabbits by a subarachnoid injection of two billion freshly isolated meningococci. The virulence was quickly lost on serum medium, but was retained for several months when the organisms were transferred

every two weeks on Dorset's medium. Very satisfactory viability (from two to three months) and virulence (from one to one and a half months) were maintained when a liquid egg medium under paraffin oil was used. Partially attenuated strains were reactivated by passage through animals, using either augmented doses or homologous endotoxin prepared by heating an emulsion at 100 C. The minimum lethal dose for a rabbit weighing 1.5 Kg. appeared to be between one and two billion organisms. The apparent virulence was dependent on the combined infectiousness of living organisms and the pathogenicity of the toxic substance, which accounted for the relatively large dose needed.

FROM THE AUTHORS' CONCLUSIONS.

REPEATED INJECTIONS OF B C G IN MONKEYS. I. M. LÉVITAN and D. D. LOKHOFF, Ann. Inst. Pasteur **50**:749, 1933.

Repeated vaccinations of monkeys with B C G were absolutely innocuous. They conferred a clearly increased resistance to subsequent virulent infections. Neither repeated vaccinations or spontaneous disease nor poor nutrition increased the virulence of B C G. The use of B C G on tuberculous monkeys exercised no noticeable effect on the evolution of virulent tuberculous processes.

AUTHORS' CONCLUSIONS.

AUTOCHTHONOUS RABIES IN AFRICA. S. NICOLAU, C. MATHIS and V. CONSTANTINESCO, Ann. Inst. Pasteur **50**:778, 1933.

There exists in the western part of the French mandate in Africa a special disease of mad dogs, in the local dialect "Oulou-fato." Several strains of the fixed virus were established in rabbits. The Negri bodies were most apparent in the basal optic nerve. The virus was invisible and was not cultured successfully. It was effective in dilutions of 1:500 (street virus) and 1:20,000 (fixed virus). Glycerin attenuated the street virus in three or four weeks, and the fixed virus, in three or four months. The substances associated with the virus were electronegative. Rabbits and guinea-pigs were more susceptible than rats, mice, dogs or chickens. Subdural inoculation with the street virus induced, in rabbits, a rabies the paralytic phase of which was preceded by a stage of excitement and intense contraction. The fixed virus induced a severe paralytic reaction of short duration. Rabbits were killed by the latter when it was injected by skin, muscle, eye or vein or in the region of the sciatic nerve. The neurotropic properties were marked. The histologic changes in the central, visceral and peripheral nervous systems were those of rabies. The Negri bodies differed in their staining properties, but were almost always blue by Mann's method, without the oxyphilous character of the cytoplasmic granules found in rabies. The pleomorphism was accentuated. Neurons in advanced stages of degeneration often had inclusions. Cross immunity for classic rabies was perfect. The extensive experimental report is accompanied by a two page color plate.

FROM THE AUTHORS' CONCLUSIONS.

TYPHUS IN RATS. CHARLES NICOLLE, Arch. Inst. Pasteur de Tunis **21**:349, 1933.

Transfer experiments with the historic strain of typhus (Tunis) in rats indicated that a silent infection might be induced by inoculation of brain material into the peritoneal cavity. A definite number of transfers, twelve or thirteen, appeared to be the limit. Transfer was effected from animals killed from the seventh to the sixteenth day after inoculation, and from four days before to two days after the appearance of fever in control guinea-pigs. Failure to propagate the virus over a longer period was attributed to a failure of the virus to adapt itself to an unnatural host.

FROM THE AUTHOR'S CONCLUSIONS.

SURVIVAL OF TYPHUS VIRUS IN BRAIN TISSUE. CHARLES NICOLLE and J. LAIGRET, Arch. Inst. Pasteur de Tunis **21**:357, 1933.

Virulent Toulon virus was present in the brains of rats for as long as sixty-eight days. The virus survived in the brains of guinea-pigs for not longer than thirty-three days. Several strains of Mexican virus were not demonstrated after fifty days in rats or thirty-four days in guinea-pigs. With the Tunis virus the situation was reversed; rats were free from the virus twenty days after inoculation, and guinea-pigs irregularly showed its presence at this time. Brains of rats given the virus of Rocky Mountain spotted fever were free from it on the twentieth day and guinea-pigs on the twenty-eighth day, but the end-point was not determined.

M. S. MARSHALL.

Immunology

TITRATION OF YELLOW FEVER VIRUS IN STEGOMYIA MOSQUITOES. N. C. DAVIS, M. FROBISHER, JR., and W. LLOYD, J. Exper. Med. **58**:211, 1933.

Titrations were made of the virus of yellow fever in mosquitoes of the genus Stegomyia, rhesus monkeys being used as test animals. Immediately after becoming engorged with highly infectious blood, the average mosquito contained between 1,000,000 and 2,000,000 lethal doses of virus. The titer of freshly ingested blood was as high as 1,000,000,000 lethal doses of virus per cubic centimeter. During the fortnight succeeding the ingestion of infectious blood there occurred a reduction of titratable virus to not more than 1 per cent of that present in the freshly fed insects. The titer was somewhat higher at later periods. This rise in titer signified possibly, not a multiplication, but merely an increase of extracellular virus and of that easily freed by grinding to a titratable form. At no later stage did the quantity of titratable virus equal that demonstrable in freshly fed insects.

AUTHORS' SUMMARY.

PRECIPITIN REACTION IN YELLOW FEVER. T. P. HUGHES, J. Immunol. **25**:275, 1933.

Serums taken from monkeys shortly after recovery from severe yellow fever infections possess a precipitin capable of reacting with a precipitinogen which occurs in the blood of monkeys during the period of acute illness. This precipitinogen is not the virus of yellow fever, but appears to be associated with a protein of the albumin fraction. Its concentration reflects the severity of the illness. It disappears with recovery, after stimulating the formation of a precipitating antibody. This resulting precipitin is entirely independent of the protective antibody resulting from an infection. A similar precipitin occurs in the serum of patients shortly after recovery from a severe yellow fever infection. This precipitin reacts with the precipitinogen occurring in the blood of monkeys during the acute phase of the illness.

AUTHOR'S SUMMARY.

THE VOLUME OF PRECIPITATE IN PRECIPITIN REACTIONS. F. S. JONES and R. B. LITTLE, J. Immunol. **25**:381, 1933.

A procedure has been described whereby the quantity of precipitate resulting from the action of precipitin and antigen can be measured. At one point in titrations, as usually practiced, the greatest quantity of precipitate is formed, and we have called this point the zone of maximum precipitation. With this as a basis we have been able to show that the quantity of precipitate varies proportionately with changes in the quantity of either antigen or immune serum. A linear type of reaction has been demonstrated. In addition, similar linear relationships have been shown in the determinations of antigen and antibody in the supernatant fluid after precipitation has taken place. We have not been able to show that in a given series of cow serum and its precipitin either the antigen or the antibody is completely utilized. When a single antigen, such as egg albumin, was employed with

its precipitin there occurred within a narrow zone complete binding of both the antigen and the antibody, while in either direction one or the other was still present in active form.

AUTHORS' SUMMARY.

EFFECT OF DISSOCIATION ON ANTIGENIC BEHAVIOR OF SALMONELLA AND SHIGELLA CULTURES. G. M. MACKENZIE and HELEN FITZGERALD, J. Immunol. **25**:397, 1933.

The antigenic components of Salmonella and Shigella may show qualitative and quantitative changes due to dissociation. Components not demonstrable in the original culture may appear in the variants. The more marked the change in the colony form, the more marked are the alterations in serologic behavior. Changes in antigenic behavior due to dissociation are qualitatively different from those caused by heat.

EDNA DELVES.

CULTURES AND BROTH FILTRATES OF STAPHYLOCOCCI. E. L. BURKY, J. Immunol. **25**:419, 1933.

Intracutaneous or intravenous injection of staphylococcus toxin into rabbits is followed by the development of an active immunity to the toxin and by the appearance of precipitating substances in the serum. The intracutaneous method is as effective as the intravenous, and the rate of mortality is less. In certain rabbits antibodies capable of passively protecting rabbits against multiple lethal doses of toxin are developed, independently of precipitins. Certain serums, supposedly immune and with high precipitin titers, seem to increase the lethal action of the toxin. The serums of rabbits immune to toxin precipitate only with the filtrates of strains of staphylococci pathogenic for rabbits. Strains of staphylococci pathogenic for rabbits have been recovered only from definite lesions in man and rabbits. This relation suggests a method for the classification of staphylococci and a diagnostic aid in cases in which staphylococci are isolated and in which the etiologic significance is doubtful.

AUTHOR'S SUMMARY.

SEASONAL CHANGES IN THE CATAPHORETIC VELOCITY AND VIRULENCE OF STREPTOCOCCI. E. C. ROSENOW, J. Infect. Dis. **53**:1, 1933.

A method yielding reliable results in the isolation of streptococci and the study of their cataphoretic velocities is described. Streptococci as isolated from atria of infection, especially from the nasopharynges of well persons and persons ill with various nonepidemic or epidemic diseases, have characteristic cataphoretic velocities and sometimes also demonstrably characteristic degrees of virulence. A striking parallelism was found between the cataphoretic velocity of streptococci isolated from the nasopharynges of persons ill with epidemic diseases, such as the common cold, influenza and poliomyelitis, and that of streptococci isolated at the same time from the raw milk supply, as well as between the velocities of both in their return to normal after the epidemics disappeared. The velocity of streptococci isolated from the nasopharynges of normal persons and that of streptococci isolated from the nasopharynges and other atria of infection, including the apexes of pulpless teeth, of persons suffering from chronic diseases such as encephalitis and arthritis shift toward that of the streptococci prevalent in the throats of persons suffering from the epidemic respiratory diseases in question, especially the common cold and influenza, and return, respectively, to the normal and to that characteristic of the chronic disease after the epidemics subside. Despite these striking revelations with respect to the etiologic importance of streptococci it is not concluded that the "virus" of the common cold or other organisms also isolated sometimes in this condition and influenza have no etiologic significance in these diseases. The increase in incidence of acute systemic diseases, such as arthritis, the exacerbations of symptoms in chronic infective diseases and the rise and fall of epidemic waves of infectious diseases according to season, in the light of these results, become more explicable.

AUTHOR'S SUMMARY.

MUCOID ENCAPSULATED STREPTOCOCCI IN SCARLET FEVER. I. PILOT and D. J. DAVIS, J. Infect. Dis. **53**:29, 1933.

Encapsulated hemolytic streptococci forming mucoid colonies on ascites blood agar were isolated in sporadic cases of scarlet fever. A strain isolated from bovine mastitis causing milk-borne epidemic scarlet fever also yielded such colonies and capsules. Certain differences are described between these streptococci of scarlet fever and Streptococcus epidemicus of septic sore throat. Toxins of these streptococci from epidemic and sporadic scarlet fever correspond to the specific toxin of the streptococcus of scarlet fever and not to the toxin of Str. epidemicus of septic sore throat. The encapsulated streptococci of septic sore throat and scarlet fever may be similar in their behavior as the cause of milk-borne infections, both producing bovine mastitis from which an outbreak of septic sore throat or of scarlet fever may develop. That such a similarity exists may be further determined by proper studies of milk-borne scarlet fever. The problem of the control of milk-borne scarlet fever then will become identical with that of the control of septic sore throat.

AUTHORS' SUMMARY.

MICRO-ORGANISMS WHICH DECOMPOSE THE SPECIFIC CARBOHYDRATE OF PNEUMOCOCCUS, TYPES II AND III. G. M. SICKLES and M. SHAW, J. Infect. Dis. **53**:38, 1933.

A description is given of several strains of soil organisms isolated from decaying organic matter in different localities which are able to decompose the specific polysaccharide of Pneumococcus, type III. One of the strains, unlike that previously described by Avery and Dubos, also utilizes agar. Experiments with the protective and curative effect, in mice, of the enzyme obtained from these strains confirmed, in general, the results of Avery and Dubos. A soil organism which decomposes the specific polysaccharide of Pneumococcus, type II, and which differs markedly from the strains that decompose the carbohydrate of Pneumococcus, type III, is also described. From this organism no soluble enzyme was obtained. Neither the specific "cellular carbohydrate" of type II nor that of type III (Wadsworth and Brown) produced purpura in mice after it had been acted on by the homologous decomposing organism.

AUTHORS' SUMMARY.

COMPLEMENT FIXATION IN VACCINIA AND IN VARIOLA. R. F. PARKER and R. S. MUCKENFUSS, J. Infect. Dis. **53**:44, 1933.

By the technic of complement fixation a specific reaction between the virus of vaccinia and the immune serum has been demonstrated. The reaction is influenced by the potency of the serum and by the time allowed for fixation, and apparently many of the failures of other workers to demonstrate it have been due to the use of serum of insufficient activity or to too short a period of fixation. Active virus in the antigen is not necessary for fixation; preparations which had been boiled or passed through a Berkefeld N candle and in which no virus could be demonstrated still fixed complement with immune serum, although not in as great a dilution as before treatment. These results are probably comparable with those obtained by Cragie in his study of the antigens taking part in the reaction of flocculation. Specific complement fixation in smallpox has also been demonstrated by using a specific antivaccinal rabbit serum and the fluid from the pustules of the disease. This has been made possible by an adaptation of the test to a small volume, the reagents being measured in drops. Various materials from persons with different cutaneous diseases and from the vesicles of varicella have been tested, without false positive results. With vaccinia and variola the results have been uniformly positive when the material was collected before the thirteenth day of the eruption. Difficulty due to bacterial contamination has been avoided by the use of serum prepared against a bacteria-free antigen. Serums from ten patients with variola were tested, with

partial or complete fixation in three. Complement fixation with a specific antivaccinal serum may be of assistance in the early diagnosis of smallpox.

AUTHORS' SUMMARY.

INFLUENCE OF HIGH FREQUENCY DISPLACEMENT CURRENTS ON BACTERIA. F. W. FABIAN and H. T. GRAHAM, J. Infect. Dis. **53**:76, 1933.

In a high frequency displacement current of 10 megacycles and an intensity of 0.08 ampere colon bacilli increased in number nearly 300 per cent during a period of three hours. When the intensity of the displacement current was increased approximately ten times the lethal effect of the current became evident. Of the three frequencies studied, 7.5, 10 and 15 megacycles, 10 megacycles was the most effective, 7.5 megacycles was the least effective, and 15 megacycles occupied an intermediate position with respect to killing action on bacteria. The high frequency displacement currents produced a regular order of death in bacteria. When the logarithm of the number of bacteria surviving at regular intervals was plotted against time a typical survivor curve resulted.

AUTHORS' SUMMARY.

DISSOCIATION OF CLOSTRIDIUM WELCHII. H. R. LIVESAY, J. Infect. Dis. **53**:125, 1933.

After prolonged cultivation on the surface of suitable artificial mediums, Clostridium Welchii produced rough colonies made up of encapsulated rods arranged in chains or filaments. From such variants there sometimes developed pigmented subsurface rootlets growing into the underlying medium. Cl. Welchii planted deep in shake tubes produced variants that formed colonies morphologically similar to the characteristic colony of Clostridium sporogenes. However, owing to the fact that it was impossible to isolate Cl. sporogenes from these colonies and to the fact that in every instance the organisms present gave the characteristic reaction of Cl. Welchii, it is believed that they were variants of the latter organism. Under certain circumstances Cl. Welchii growing on the surface of solid mediums produced pigmented subsurface rootlets or colonies; in shake cultures, this clostridium sometimes grew as ball-shaped colonies. The results indicate that pigmentation and subsurface penetration do not always mean contamination, but may result from dissociation of Cl. Welchii.

AUTHOR'S SUMMARY.

THE SHWARTZMAN PHENOMENON. A. M. PABST and S. E. BRANHAM, Pub. Health Rep. **48**:639, 1933.

Serum neutralization of the Shwartzman phenomenon produced by filtered meningococcic washings is not restricted to antimeningococcic serums, but also occurs with antipneumococcic, antidysenteric and antigonococcic serums and with diphtheria antitoxin, as well as with normal horse and rabbit serums. This nonspecific neutralization is so frequent and so marked that it seems to limit the usefulness of the Shwartzman phenomenon in the evaluation of therapeutic antimeningococcic serums.

AUTHORS' SUMMARY.

IMMUNOLOGICAL STUDIES WITH PHAGE-COATED BACTERIA. F. M. BURNET, Brit. J. Exper. Path. **14**:93, 1933.

Bacteria on which certain bacteriophages have been adsorbed can be specifically agglutinated by antibacteriophage serum and can be used to absorb antibacteriophage from an immune serum. Cross-absorption experiments by this technic have been carried out with two antigenically related bacteriophages and their antiserums. With one bacteriophage it has been shown that bacteriophage inactivated by a solution of formaldehyde can be adsorbed by bacteria and endow them with the specific reactivity toward the corresponding antibacteriophage.

AUTHOR'S SUMMARY.

A Specific Soluble Substance from Bacteriophages. F. M. Burnet, Brit. J. Exper. Path. **14**:100, 1933.

A bacteriophage-specific soluble substance is present in bacteriophage-free ultrafiltrates of lysed cultures; it can be demonstrated by its blocking effect on the specific bacteriophage-antibacteriophage reaction. The specific soluble substance is not adsorbed by bacteria sensitive to the corresponding bacteriophage and does not represent a soluble lysin. The activity of the specific soluble substances is reduced by heating to temperatures above 65 C., and is completely lost after heating for thirty minutes at from 90 to 93 C. By the addition of relatively large amounts of the specific soluble substances to bacteriophage-antibacteriophage mixtures the process of neutralization can be stopped and to some degree reversed. Rabbits inoculated with ultrafiltrates containing the specific soluble substances show a slight appearance of bacteriophage-inactivating antibodies.

Author's Summary.

Immunological Studies with the Virus of Psittacosis. S. P. Bedson, Brit. J. Exper. Path. **14**:162, 1933.

The serums of persons convalescent from psittacosis possess no demonstrable neutralizing power, but will fix complement in the presence of a psittacosis antigen. Similarly, the serums of hyperimmunized guinea-pigs contain considerable antibody strength demonstrable by complement-fixation or agglutination tests, but only a low neutralizing power. The value of the complement-fixation reaction in the diagnosis of psittacosis is discussed. Virus which has been rendered inactive by means of a solution of formaldehyde can produce a considerable degree of immunity in mice. Virus to which a solution of formaldehyde has been added can be steamed for twenty minutes without much loss of immunizing power, but steaming alone has a deleterious effect.

Author's Summary.

Hay Fever Reagin-Allergen. D. Harley, Brit. J. Exper. Path. **14**:171, 1933.

Mixtures of reagin and allergen produce reactions in normal skins. Reagin is not inactivated by allergen in vitro. Allergen is bound by reagin in vitro. Allergen bound by reagin can be freed by heating to destroy the reagin.

Author's Summary.

The Toxic Effects of Staphylococcal Filtrates Introduced Enterally. Grizel R. Borthwick, Brit. J. Exper. Path. **14**:236, 1933.

When staphylococcus toxin is added to gastric contents in vitro a slightly acid (p_H 6.8) or a slightly alkaline (p_H 7.8) reaction impairs its activity, whereas no inactivation occurs at p_H 7.3. Symptoms of poisoning can only occasionally be produced in guinea-pigs and rabbits when toxin is introduced directly into the stomach. Uniformly positive results are obtained in experiments in which the reaction of the stomach is adjusted to p_H 7.3 at the time the toxin is introduced. The animals die within five days, and postmortem signs of acute gastro-enteritis and marked congestion of internal organs, associated with hemorrhage in the stomach and kidneys, are evident. Symptoms of poisoning can be produced by intrarectal inoculation of toxin when the rectum has been irrigated with saline solution and the reaction adjusted to p_H 7.3. Postmortem features are similar to those obtained after introduction of toxin into the stomach. This method is not so effective as inoculation into the stomach.

Author's Summary.

The Enzymes of the Agalactia Virus. A. Pirie and B. E. Holmes, Brit. J. Exper. Path. **14**:290, 1933.

The virus of Agalactia, when centrifugated out of a culture, can be shown to reduce methylthionine chloride, U. S. P. (methylene blue) in the presence of lactate, broth or serum. Growth of the virus in culture can be demonstrated by the

increased rate of reduction of methylthionine chloride by a measured amount of culture. A culture of Agalactia shows a large uptake of oxygen, and so also does a saline suspension of the virus in the presence of lactate or of broth. The dehydrogenase and oxidative systems are extremely sensitive to mechanical agitation. A saline suspension of the virus loses all its reducing capacity after air or nitrogen has been bubbled through it, or air in the presence of cyanide. The number of viable organisms is also much reduced. Broth has a protective effect on the enzymes and the viability. It is suggested that these facts may be of importance in connection with the filtrability of some other viruses. The enzyme activity and the viability are greatly reduced by exposure to light in the presence of very small amounts of methylthionine chloride. No change can be shown in the distribution of nitrogen in a culture during growth, and no disappearance of dextrose can be detected. There is nearly always a small decrease in lipoid phosphorus during growth.

AUTHORS' SUMMARY.

AGGLUTININS WITH TYPHOID-PARATYPHOID VACCINE. G. GIGLIOLI, J. Hyg. **33**:387, 1933.

The author's results confirm Gardner's views: Inoculation with typhoid-paratyphoid organisms gives rise to somatic agglutinins. This reaction is marked in the first few weeks after vaccination, but it is always limited to low and medium dilutions; the highest titer for a positive result in this series, with an "O" antigen, was 1:320. In actual enteric infection "H" agglutinins are higher than "O"; but "O" titers are higher in patients with enteritis than in vaccinated subjects. In four cases of typhoid and in twelve of paratyphoid C, "O" agglutinins were found after the first week in dilutions from 1:80 to 1:2,560, and appeared earlier in the disease than the "H" agglutinins. "O" agglutinins in vaccinated subjects do not destroy the qualitative receptor analysis in the serologic diagnosis; quantitatively the end-titer must be established. Diagnosis by serologic methods within three months after inoculation is uncertain. After this period the presence of "O" agglutinins in high dilutions is suggestive of active infection, and negative results of tests have little value unless confirmed.

EDNA DELVES.

MULTIPLE TOXINS PRODUCED BY SOME ORGANISMS OF THE CL. WELCHII GROUP. A. T. GLENNY and others, J. Path. & Bact. **37**:53, 1933.

Culture filtrates of "Bacillus paludis" and the lamb dysentery bacillus contain at least four toxins for each of which there is a specific antitoxin. The existence of these toxins has been demonstrated by means of titrations by different methods against a number of serums. This has revealed the deficiency, in certain serums, of one or more of the specific antibodies. The relative proportions of each antibody in a serum depend chiefly on the normal antitoxic content before immunization of the horse providing the serum. The intravenous method of testing mice does not measure any single toxin-antitoxin reaction.

AUTHORS' SUMMARY.

SPECIES IMMUNITY TO VIRULENT STREPTOCOCCI. H. B. DAY, J. Path. & Bact. **37**:169, 1933.

When their virulence is exalted, streptococci become resistant to phagocytosis and to extraction with acid. Their agglutination reactions with antiserums are also modified. These properties of virulent streptococci appear to be due to their power of forming a special material which is antigenic. This special antigen is common to the species and is formed by streptococci of different types—both hemolytic and nonhemolytic. In broth cultures this antigen is formed only by highly virulent strains during the phase of active growth and is almost entirely attached to the cocci. In serum-broth cultures this antigen is also present in the culture fluid and persists longer. This species or "V" antigen resembles other antigens of pyogenic cocci in that it is: (*a*) resistant to acid, (*b*) destroyed on

heating in an alkaline medium, (*c*) destroyed by exposure to the action of bacterial enzymes and (*d*) readily adsorbed to protein on precipitation of the latter. Injection of V antigen excites active immunity to all virulent streptococci, hemolytic and nonhemolytic, while the serums of animals so treated confer passive immunity.

AUTHOR'S SUMMARY.

A SIMPLE METHOD FOR PREPARATION OF SPECIFIC SOLUBLE SUBSTANCE OF TYPE I PNEUMOCOCCUS. H. W. DUDLEY and W. SMITH, J. Path. & Bact. **37**:341, 1933.

The method depends on the precipitation of the specific polysaccharide from aqueous solution by 1.5 volumes of 96 per cent alcohol, repeated precipitation eliminating most of the accompanying contaminations. It is said to be a reliable method.

THE SEROLOGICAL GROUPING OF THE STARCH FERMENTING STRAINS OF C. DIPHTHERIAE. J. O. EWING, J. Path. & Bact. **37**:345, 1933.

One hundred and six starch-fermenting strains of Corynebacterium diphtheriae have been serologically tested and found to comprise five distinct types. The members of types A, B and D conform to the original description of the gravis organisms. Those of type C have an "atypical" colony form by which they may usually be distinguished. The fifth type (X) did not conform culturally to the description of the gravis organisms. The fifty strains which did not ferment starch were found to be serologically distinct from the starch-fermenting strains.

AUTHOR'S SUMMARY.

ANTIHAEMOLYTIC TITRE OF SERUM FOLLOWING STAPHYLOCOCCAL INFECTION. J. I. CONNOR and M. MCKIE, J. Path. & Bact. **37**:353, 1933.

Our results indicate that though there is much individual variation, superficial infection in man is accompanied in a high proportion of cases by a rise in the antihemolytic titer of the serum. The results of the treatment in these cases by injection of toxoid, recorded elsewhere, show that a rise in antihemolytic titer accompanies improvement or cure. We are not, however, prepared to assume that these parallel observations are necessarily correlated, and the improvement in clinical condition may be due to allergic desensitization or to some other cause. In three cases of pyemia in man a high antihemolytic titer was found—it was highest in one who survived the infection—but in the artificially immunized animals there was no clear relationship between the antihemolytic titer of the serums and indefinite or prolonged survival following the intravenous injection of living virulent staphylococci. It is, however, of interest that three animals indefinitely survived the intravenous injection of 0.5 cc. of a virulent broth culture of staphylococci.

AUTHORS' DISCUSSION.

SPECIFICITY OF BACTERICIDAL PROPERTIES OF NORMAL SERUM. M. H. FINKELSTEIN, J. Path. & Bact. **37**:359, 1933.

A nonspecific soluble factor is present in suspensions of heated bacterial cultures which may produce inhibition of the bactericidal action of normal serum. Nonspecific results sometimes obtained when normal guinea-pig serum is "adsorbed" with a bacterial culture and then tested for bactericidal properties are apparently due to this factor. Such effects may obscure the specific absorption of a natural bactericidal antibody by the bacterial antigen. Some samples of guinea-pig serum are unaffected by this factor at 0 C. but are susceptible to it at a higher temperature, e. g. 15 C. The inhibitory reaction produced by this factor is relatively slow as compared with specific absorption.

AUTHOR'S SUMMARY.

THE BACTERICIDAL POWER OF NORMAL SERUM. J. GORDON, J. Path. & Bact. **37**:367, 1933.

Adsorption of both normal and heated serums by dead bacteria fails to yield any evidence for the existence of a series of specific antibodies in serum. The loss of bactericidal power consequent on adsorption is never specific for the adsorbing organism but is always general. The behavior of adsorbed heated serum is especially important. This is also true of pig's serum in spite of the fact that pig's serum contains some specific agglutinins. It was not found possible to demonstrate any sensitization of living bacteria by heated serum. The results recorded in this article lead to the belief that bactericidal activity is the result of the joint action of complement and a nonspecific heat-stable intermediary factor. It is believed that this factor is adsorbed by the bacteria, but that possibly, owing to its nonspecific character, the adsorption is only feeble and is not necessarily a primary adsorption. The experimental demonstration of such an adsorption would therefore be difficult.

AUTHOR'S SUMMARY.

TUBERCULOUS BACILLAEMIA. G. S. WILSON, Medical Research Council, Special Report Series, no. 182, London, His Majesty's Stationery Office, 1933.

Critical examination of available records leads to the conclusion that tuberculous bacillemia is far less frequent than has been claimed by many workers. It appears that bacillemia of an intensity sufficient to be detectable by present methods of examination is, except as a transitory phenomenon, rarely present in tuberculosis until the disease has assumed a more or less acute phase accompanied by extensive lesions or by actual generalization. It is present, perhaps, in from 5 to 10 per cent of cases of severe, advanced and progressive pulmonary disease and in from 30 to 40 per cent of cases of miliary and meningeal tuberculosis. In the cardiac blood of patients who have died of tuberculosis, postmortem examination may be expected to reveal the presence of tubercle bacilli in about 50 per cent of the cases. There is practically no evidence that a tuberculous bacillemia ever occurs in such diseases as articular rheumatism, polyarthritis, chorea, multiple sclerosis, schizophrenia, retrobulbar neuritis, Hodgkin's disease and certain diseases of the skin in the absence of gross lesions of tuberculosis, nor are there any sound reasons to suppose that the tubercle bacillus plays any essential rôle in the etiology of these diseases. The excessive numbers of positive results recorded by some workers are attributable to the failure to realize, or to pay adequate attention to, the numerous fallacies attending the demonstration of the tubercle bacillus. In this connection may be mentioned: (*a*) the occurrence in lysed blood of acid-fast particles closely resembling tubercle bacilli; (*b*) the failure to take the elementary precautions necessary to avoid confusion caused by the use of old slides, of blotting paper or of contaminated cedar-wood oil; (*c*) the impossibility, on microscopic grounds alone, of distinguishing the tubercle bacillus from saprophytic acid-fast bacilli that may gain access to preparations of suspected material from such situations as water, dust, excreta, sebaceous material and animal fodder, in which they are often abundant; (*d*) the assumption that macroscopic colonies of acid-fast bacilli appearing in culture are necessarily those of tubercle bacilli; (*e*) the diagnosis of tuberculosis in guinea-pigs following inoculation, on insufficient grounds, such as a microscopic demonstration of acid-fast bacilli in viscera of animals showing no macroscopic lesions or in the local lesion or regional lymphatic glands of animals showing no other evidence of the disease, or such as macroscopic lesions due either to spontaneous tuberculosis or to Salmonella, Pasteurella, Brucella or pyogenic infections, or such as a reaction to tuberculin in an animal that is found at autopsy to show no signs of tuberculous disease. In regard to the work of Löwenstein, it is impossible on the evidence presented to accept the far-reaching conclusions, both of fact and of theory, that he has put forward. There is, moreover, no reason to believe that isolation of the tubercle bacillus from the blood is likely to be of any practical value in the early diagnosis of tuberculosis.

FROM THE AUTHORS' SUMMARY.

PRECIPITIN REACTIONS IN THE BLOOD OF RHEUMATIC PATIENTS FOLLOWING ACUTE THROAT INFECTIONS. B. SCHLESINGER and A. G. SIGNY, Quart. J. Med. **2**:255, 1933.

Streptococcic precipitins can be demonstrated in the blood of rheumatic patients following acute streptococcic infections of the throat. Their formation is delayed until from the second to the fourth week from the onset of the nasopharyngeal infection (the end of the silent period), and their appearance in most cases foreshadows a tendency to a relapse of acute rheumatism. The precipitin corresponds to the type of streptococcus responsible for the infection, but a certain amount of formation of cross-precipitin may occur. The formation of precipitin is regarded as one of the manifold reactions which take place in the patient's defense mechanism during the silent period. Time is thus available for prophylactic measures if the infection of the throat has not passed unnoticed. Concentrated acetylsalicylic acid therapy during this period undoubtedly prevents serious relapses in many cases. It is not infallible, and further researches for a more reliable method are urgently required.

AUTHORS' CONCLUSIONS.

PARASPECIFIC IMMUNITY FROM B C G. A. CALMETTE and A. SAENZ, Ann. Inst. Pasteur **50**:433, 1933.

Experimental and clinical observations have demonstrated that four or five weeks following the injection or ingestion of B C G vaccine there exists an immunity to diseases other than tuberculosis, notably to streptococcic, pneumococcic, brucella and anthracotic infections. Calmette and Saenz believe that this accounts for the general reduction in mortality from all causes in vaccinated infants.

FROM THE AUTHORS' CONCLUSIONS.

ASYMPTOMATIC ANTHRACIC INFECTION IN MAN. G. J. SINAI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:199, 1933.

The population of a camp of Kossacks ate veal from a calf killed while it was sick with anthrax. Only one participant contracted the disease; he recovered in twelve days. Precipitation tests according to Ascoli were carried out on the other members of the tribe and on many inhabitants of the region. The blood serums of the tested persons were employed as antigen with a precipitating serum known to be specific. The result with the serums of fifteen of the thirty-eight tested persons was positive. Thirteen of the persons whose serums reacted positively ate the infected meat while of the 23 whose serums reacted negatively 17 ate the meat. The serums of a large number of the controls reacted negatively. Sinai concludes that consumption of meat infested with Bacillus anthracis may lead to an asymptomatic form of the disease. The positive reaction of the serums of a few persons was found to have become negative after one month's interval.

I. DAVIDSOHN.

INFLUENCING RESISTANCE TO BACILLUS COLI WITH OTHER BACTERIA. S. NUKADA and K. FUJII, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:287, 1933.

One hundred and twenty-two rabbits were treated with cultures of fifteen different bacterial species and on the tenth day after the last injection were given a fatal dose of a highly virulent culture of Bacillus coli. Their resistance was markedly increased by treatment with cultures of Bacillus proteus, Bacillus pyocyaneus and Bacillus typhosus, and to a lesser extent by treatment with cultures of Bacillus paratyphosus A and B, Bacillus pertussis, Bacillus pestis and Meningococcus; it was lowered by treatment with cultures of pneumococcus, Staphylococcus, Bacillus influenzae and Bacillus dysenteriae. The resistance of the rabbits was not altered by treatment with cultures of Gonococcus, Streptococcus and Vibrio cholerae. The influence was assumed to be of a nonspecific nature.

I. DAVIDSOHN.

SUPRARENAL GLAND AND INFECTION. H. LANGECKER and E. SINGER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:326, 1933.

Suprarenal cortex and liver fed to mice for seven days increased their resistance to streptococcic and pneumococcic infections. Extracts of the organs acted similarly, but only if proper quantities were injected. Suprarenal cortex proved more potent than liver. The resistance of guinea-pigs to tuberculosis and typhus fever was not influenced.

I. DAVIDSOHN.

Tumors

EXPERIMENTAL STUDIES ON LYMPHOMATOSIS OF MICE. J. FURTH, H. R. SEIBOLD and R. R. RATHBONE, Am. J. Cancer **19**:521, 1933.

Leukemic lymphomatosis (lymphoid leukemia), aleukemic lymphomatosis, lymphosarcoma and leukosarcoma are malignant processes; they are different manifestations of the same disease. Two factors are chiefly concerned in determining the type of the disease: (1) the possibility of free entrance of malignant lymphocytes into the circulation; (2) the character of the malignant lymphocyte. These factors alone are not quite sufficient to explain the individual variations of the blood involvement and of the localization of lesions in animals inoculated with the same strain. Lymphomatosis is transmissible to healthy animals, the success of transmission depending on the transfer of viable cells. Blood cells readily transmit lymphomatosis of mice, but cell-free plasma fails to transmit the disease. Procedures which destroy these cells but which fail to affect most viruses, such as adding glycerin or drying, inactivate the transmitting agent. Malignant lymphocytes are well preserved at low temperatures, and when kept in an icebox at + 4 C. for as long as seven days transmit the disease, but at temperatures below — 20 C. these cells are destroyed in thirty minutes. At incubator temperature, namely 37.5 C., they lose their transmitting power in from three to twenty-four hours. Leukemic lymphocytes are not lymphoblasts but malignant (pathologic) lymphocytes with limited power of maturation, and when these cells multiply, their characteristics persist. These characters determine their ability to produce tumors, to invade the blood stream, to transmit the disease to related or unrelated mice, to localize in certain organs, etc. The essential change in leukemia consists not in the appearance of immature blood cells in the circulation (analogous to the "shift to the left" of Arneth) but in the invasion of the blood stream by malignant lymphocytes. The success of inoculations depends on the characters of the malignant lymphocytes persisting through successive passages, as well as on external factors such as the dose, the route of entry and the resistance of the mice. Furthermore, successful inoculation is dependent on an inherited susceptibility of the host. A single exposure to x-rays is sufficient to destroy the resistance of insusceptible mice to implantation of leukemic cells. The smallest quantity of irradiation that brings about this change is approximately 30 roentgens, and the percentage of successful inoculations increases with the quantity of irradiation. The duration of increased susceptibility depends on the quantity of x-rays used, and mice exposed to sublethal doses of x-rays may remain susceptible for three months. Irradiation of mice with sublethal doses immediately after inoculation does not destroy all the malignant cells that have been introduced and does not prevent fatal disease, but prolongs the duration of the illness by from 20 to 50 per cent, probably by partial destruction of the malignant cells.

FROM THE AUTHORS' CONCLUSIONS.

HEMANGIO-ENDOTHELIOMA OF THE LIVER. RALPH H. KUNSTADTER, Am. J. Dis. Child. **46**:803, 1933.

A white girl, weighing a little more than 8 pounds (4,428 Gm.) at birth, although showing persistent extreme pallor, seemed to develop normally until 6 weeks of age, when progressive enlargement of the abdomen began. Attacks of dyspnea and cyanosis occurred, anemia appeared, and later, constipation and recurrent vomiting. Exploratory operation at 5 months of age revealed a greatly

enlarged liver extending down on the right side to the iliac crest and on the left to the level of the umbilicus. The surface of the liver was covered with numerous purplish-red nodules varying in size from that of a pea to that of a walnut. They were soft and somewhat fluctuant. On aspiration a bloody fluid was obtained. Death occurred in twenty-four hours. The liver weighed 765 Gm. On section many of the nodules consisted of cystlike spaces filled with partially clotted blood. Microscopically, the hepatic tissue, which showed marked fatty changes, was compressed by groups of flattened or cuboid endothelial cells which lined networks of vascular spaces of varying sizes. In some areas the lining cells formed papillary ingrowths; in others, they had proliferated in compact masses. In many fields the vascular spaces were found within the hepatic parenchyma with no tendency toward formation of a capsule. Metastases were not found. Fourteen other cases of hemangio-endothelioma of the liver were found in reviewing the literature. Metastases occurred in 33 per cent of these cases.

RALPH FULLER.

THE CANCER CELLS OF SEROUS EFFUSIONS. G. S. GRAHAM, Am. J. Path. **9**:701, 1933.

Neoplastic cells are readily demonstrable in pleural and peritoneal transudates resulting from neoplastic disease of the serosae. They are of interest not only because of their immediate value in clinical diagnosis but also because of the opportunity they afford for cytologic study. The tumor cells are believed to proliferate more or less actively within the fluid in which they are suspended. They occur as single cells or as clumps showing a more or less marked tendency toward organoid arrangement. Tumor giant cells occur not infrequently and may be present in large numbers. While their formation probably depends on unfavorable conditions of growth, the phenomenon may be for the individual cells a purposeful and protective mechanism. These giant cells appear to result from successive fusions between individual cells, with the gradual building up of great nuclear masses of varying form. It is suggested that multipolar mitosis is a result rather than a cause of giant and multiple nucleation of tumor cells. Multipolar mitosis is followed in some cases by cellular disintegration. No figures definitely identifiable as phases of nuclear reconstruction after multipolar mitosis have been seen in the present preparations.

AUTHOR'S SUMMARY AND CONCLUSIONS.

CELL CHANGES IN THE ANTERIOR HYPOPHYSIS AFTER CANCER IMPLANTATION IN RATS. M. F. GUYER and P. E. CLAUS, Anat. Rec. **52**:225, 1932; **56**:373, 1933.

Bits of rat carcinoma transplanted to young rats of our stock developed into active cancer in from 80 to 90 per cent of these animals. Much the same structural and physiologic changes occurred in the anterior lobe in the cancerous rats as follow castration of either males or females, namely, increased number of basophilic cells, vacuolation of basophilic cells and increased potency of the transplanted substance in stimulating ovarian size and sexual precocity. A Golgi-like apparatus was prominent in both the basophilic and the oxyphilic cells. This apparatus was closely associated with the formation of the vacuolar material of the basophilic cells in both the cancerous and the castrate rats. A distortion of the nucleus—usually an indentation on the side turned toward the Golgi-like apparatus—occurred in the larger and presumably older basophils of both the castrates and the cancerous rats; this condition was much more prevalent in the cancerous rats. That some influence emanating from the cancerous growth operated directly on the pituitary anterior lobe instead of through a sterilizing effect on the gonad is indicated by the following facts: (*a*) The estrual cycle showed little or no irregularity and cancerous animals mated and bore young. (*b*) No follicular atresia was found in rats with even advanced cancer. (*c*) Transplanted substance from the anterior lobes of cancerous castrates was more potent in stimulating ovarian growth and sexual precocity in immature rats and mice than was that from the anterior lobes of mere castrates.

Following implantation of the Flexner-Jobling carcinoma in the uteri of rats there was a slight increase in the number of oxyphilic cells in the anterior lobes of their pituitary bodies. The histologic picture was the same as that associated with pregnancy or with injections of estrin. Following such implantation in castrated females there was not so great an increase in the number of oxyphilic cells. Daily injections of 4 rat units of a water-soluble preparation of estrin (theelin) did not prevent the formation of castration cells in the hypophysis of either the castrated animal or that with subcutaneous cancer, although such treatment kept the females in a state of almost continuous estrus. The estrual cycle continued in rats with transplanted uterine carcinoma and sections of the ovaries of such rats disclosed the usual histologic picture of the nonpregnant rat.

FROM THE AUTHORS' SUMMARIES.

SPHENO-OCCIPITAL CHORDOMA. MEYER CANTOR and LOUIS D. STERN, Arch. Neurol. & Psychiat. **30**:613, 1933.

Chordoma from the notochordal remnants may be an accidental finding; that is, it may give no symptoms, or it may give a variety of clinical pictures, depending on the location. In the case reported the clinical picture was made up of pain (aching) in the right half of the face, decrease of visual acuity in the right eye and signs of a slight involvement of the third nerve with those of increased intracranial pressure (absence of the posterior clinoid processes). A mass was seen pushing into the oral cavity from the right palatal region. It protruded externally in the region of the zygomatic process of the maxillary bone. There were loss of taste in the anterior part of the tongue, immobile palate, dysphagia and anesthesia of the right half of the face. Necropsy revealed a tumor protruding from the right palatal region into the oral cavity. It filled the right orbital and nasal cavities and the maxillary, ethmoid and sphenoid sinuses, destroyed most of the base of the skull and pressed on the right hemisphere, involving the second, third, fourth, fifth, sixth and seventh nerves. The tumor was vascular; calcium salts were deposited in the septums which divided the tumor into lobules. These contained physaliform cells, which were arranged in columns and were mostly vacuolated. Many of the vacuoles contained shrunken cells that resembled cartilage cells. There were no metastases.

G. B. HASSIN.

ASTROCYTOMA OF THE CEREBELLUM: SURVIVAL FOR FORTY-FIVE YEARS WITHOUT OPERATION. L. HAUSMAN and L. STEVENSON, Arch. Neurol. & Psychiat. **30**:1100, 1933.

The first symptoms of cerebellar tumor appeared between the ages of 6 and 8 years, but the diagnosis of tumor of the brain was not made until the age of 16. For twenty-five years following antisyphilitic treatment with mercury and iodides the patient was practically well, notwithstanding that neither the marital history nor the serologic studies revealed syphilis. Occasional relapses could be controlled by antisyphilitic treatment. For two years before death the cerebellar, mainly the mental, symptoms became uncontrollable. Necropsy revealed a fibrillary astrocytoma of the fourth ventricle with cystic formations, which extended into the right and partly into the left hemisphere of the cerebellum. Another cystic cavity took the place of the sylvian aqueduct, and the third ventricle was distended and both foramina of Monro were enlarged. The pathologic conditions found at necropsy are assumed to date back to childhood.

G. B. HASSIN.

NASOPHARYNGEAL CARCINOMA. O. CHRISTIANSON and S. W. MCARTHUR, Arch. Surg. **27**:1109, 1933.

Three primary nasopharyngeal carcinomas with metastases to the cervical lymph nodes are described. The diagnosis for each patient was made clinically by examination of surgically excised tissues, and the body of one was examined post mortem. Histologically, all the tumors resembled immature squamous or pseudostratified epithelium, but in one the cells tended markedly to assume the arrangement and

structure of squamous epithelium. An essential clinical feature was the insidious and painless bilateral enlargement of the cervical lymph nodes due to metastases. The bilateral distribution of the metastases resulted from the midline location of the primary tumor and the dissemination of the growth into the lymphatics on both sides of the neck. Slight variations in cellular structure occurred in these carcinomas, but the variations were within the limits of the varieties of cells found in the pseudostratified epithelium lining the nasopharynx.

AUTHORS' SUMMARY.

COMPLEMENT FIXATION TEST IN CARCINOMA. W. SAPHIR and NELL HIRSCHBERG, J. Immunol. **25**:439, 1933.

The complement-fixation test has been studied in twenty-seven serums of cancerous patients and eighty-two control serums. The tests were positive in 77.7 per cent of the serums of cancerous patients. Only one of the eighty-two control serums, that from a patient with lobar pneumonia, gave a positive reaction. The authors are of the opinion that the reaction is physicochemical and due to the influence of the antigen on the globulins in the serum, rather than a specific antigen-antibody reaction. The clinical value of the reaction awaits further observation after refinement and after attainment of a better understanding of the nature and limitations of the test.

AUTHORS' SUMMARY.

SPECIFICITY OF IMMUNITY ELICITED BY MOUSE SARCOMA. H. B. ANDERVONT, Pub. Health Rep. **48**:1472, 1933.

Acquired immunity induced by propagable tumors is known to be effective against other transplantable growths. The purpose of the experiments recorded in this paper was to continue the earlier investigations pertaining to the specificity of the immunity elicited by sarcoma 180. The results attending the previous investigation and those recorded in this communication may be summarized as follows: 1. Sarcoma 180 induces resistance in mice which is effective against carcinoma A, carcinoma 63 and carcinoma 206. 2. It fails to induce any pronounced resistance to sarcoma 37. 3. Growth of carcinoma A, carcinoma 206 or sarcoma 37 in the mouse's tail elicits concomitant immunity in a considerable percentage of instances. However, the resistance induced by any of these tumors is not effective against sarcoma 180.

AUTHOR'S SUMMARY.

THE FUJINAMI MYXOSARCOMA IN DUCKS. W. J. PURDY, Brit. J. Exper. Path. **14**:297, 1933.

Normally, adult ducks recover from a Fujinami infection and are then solidly immune to the disease. It has now been shown that this immunity to subsequent infection is well developed by the third day, and that immunity becomes complete within the following few days. It has now been shown, too, that Rous sarcoma no. 1 growing in a duckling does not induce immunity to a Fujinami infection.

AUTHOR'S SUMMARY.

TUMORS OF THE TESTIS. A. PRUSZCZYŃSKI, Virchows Arch. f. path. Anat. **290**:137, 1933.

Pruszczyński describes four malignant tumors of the testis and presents a general consideration of testicular neoplasms based on the French and German literature. Tumors of the testis may be simple, mixed or teratoid. The simple tumors may be benign or malignant epithelial neoplasms or benign connective tissue tumors. The occurrence of sarcoma of the testis is doubtful. The malignant epithelial growths are divided into those with origin from the wolffian duct, of which one is described, and those originating in the seminal tubule epithelium. Tumors of the latter division he subdivides into seminomas of mesoblastic type, of spermatogonial type, of Sertoli cell type and of mixed type. The seminomas of mesoblastic type are composed of small, deeply stained cells derived from the undifferentiated mother cells of the tubules of the developing testis. Pruszczyński

describes one such tumor in the cryptorchid testis of a pseudohermaphrodite. The other two neoplasms which he describes in detail were spermatogonial seminomas. He appends descriptions of a benign and a malignant teratoma of the testis. He does not accept the view of French authors that such tumors arise from the primitive kidney. O. T. SCHULTZ.

MYELIN SHEATHS IN GANGLIONEUROMAS. B. KARITZKY, Virchows Arch. f. path. Anat. **290**:161, 1933.

Three immature and four mature ganglioneuromas of a series of eighteen were especially examined for the presence of myelin sheaths. Sheaths were found in all the number varying with the degree of maturity of the tumor tissue. The sheaths were new formed. Their formation began in the more mature parts of the tumor and usually about blood vessels. O. T. SCHULTZ.

CAVERNOUS HEMANGIOMA OF THE SUPRARENAL GLANDS. M. MÜLLER-STÜLER, Virchows Arch. f. path. Anat. **290**:177, 1933.

The condition described was an accidental finding at the necropsy of a woman aged 77 years. The suprarenal glands measured, respectively, 6.4 by 4.2 by 1.8 cm. and 6 by 3.5 by 1.3 cm. Each consisted predominatingly of cavernous blood spaces, in some of which thrombosis and calcification had occurred. The condition is held to have been due to congenital maldevelopment. No symptoms referable to the suprarenal glands had been noted during life. O. T. SCHULTZ.

SEROLOGIC DIFFERENTIATION BETWEEN GLIOMATOUS AND NORMAL CEREBRAL PARENCHYMA. H. REICHNER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:85, 1933.

In complement-fixation tests, the serum of one of three rabbits treated with gliomatous tissue reacted specifically with the homologous antigen (glioma), permitting a sharp differentiation of gliomatous from nondiseased cerebral tissue. Serum immunized against normal brain tissue reacted with normal as well as with neoplastic cerebral tissue. Some antiserums produced with gliomatous tissue had the properties of organ-specific antiserums. Attempts to make the antitumor serum absolutely specific by adsorption with brain tissue failed, because this removed all the antibodies. I. DAVIDSOHN.

RELATION BETWEEN FOWL LEUKOSIS AND SARCOMA. A. R. MEYER and J. ENGELBRETH-HOLM, Acta path. et microbiol. Scandinav. **10**:380, 1933.

Erythroblastosis and myelosis of fowls are related to transmissible fowl sarcoma. The authors worked with a strain possessing both erythroblastic and sarcomatous properties. Intravenous injection of the material caused erythroblastosis; intramuscular administration induced sarcoma. Among seventy-two fowls with induced erythroblastic reactions there were fourteen with typical erythroblastic leukoses. There were sixty fowls with induced fibrosarcoma of characteristic destructive power. In twenty-one instances there were both sarcoma and erythroblastoma after intramuscular injection of the fresh tissue. In the viscera, endotheliomatous and angiosarcomatous changes were found. These changes are ascribed to action of the agent on immature mesenchymal cells (hemohistioblasts). JACOB KLEIN.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Jan. 8, 1934

E. H. HATTON, *President, in the Chair*

OCCURRENCE AND SIGNIFICANCE OF GERMINAL CENTERS (FLEMMING) IN THE HUMAN SPLEEN. PAUL R. CANNON.

An examination of 416 human spleens was made with especial reference to the so-called germinal centers in the malpighian corpuscles. The object was to learn whether the secondary nodules are centers for the production of lymphocytes or centers of reaction to pathologic stimuli. The secondary nodules (more lightly stained areas composed of cells other than small lymphocytes) were arranged in three groups: (1) those consisting largely of fragmented lymphocytes, or polymorphonuclear leukocytes; (2) those composed predominantly of reticulum cells, and (3) those in which hyaline material was conspicuous.

Forty-four of the spleens contained such secondary nodules in considerable numbers. In the other 374 spleens, or 90 per cent, the malpighian corpuscles consisted largely of small lymphocytes. Of the abnormal secondary nodules, ten belonged to group 1, twenty-nine to group 2, and five to group 3. The secondary nodules occurred in patients varying in age from 5 months to 72 years, but about two-thirds of them in persons under 35 years of age. Practically all occurred in patients suffering from severe acute or chronic infectious or toxic diseases such as acute rheumatic fever, ulcerative endocarditis, generalized tuberculosis, generalized peritonitis, acute leptomeningitis, acute bilateral otitis media, glomerulonephritis or acute toxic necrosis of the liver. None or only occasional ones were found in patients who had died from carcinoma, either localized or generalized, lymphatic leukemia, Hodgkin's disease or hypertension.

Special stains, particularly Mallory's connective tissue stain and hematoxylin-eosin-azure, indicated that the "centers" in group 1 represented areas of acute localized inflammation, whereas those in groups 2 and 3 represented proliferative reactions with the formation of collagen or hyalin. Amyloid changes were also included in this group. Large and medium-sized lymphocytes were inconspicuous in all of the three groups.

These findings suggest that the tissue reactions described represent exudative and proliferative responses of lymphoid tissues to pathologic stimuli rather than centers for the active production of lymphocytes and add further evidence to the hypothesis of Hellman that they should be regarded more as "reaction centers" than as "germinal centers."

DISCUSSION

P. A. DELANEY: Did you have an opportunity to study developing germinal centers of the lymph nodes?

P. R. CANNON: No: only those in the spleen. Most studies have been made on lymph nodes.

P. A. DELANEY: As regards the question whether they were endothelial or lymphatic germinal centers, it is important to state that reticulocytes are not lymphoblastic.

MONOCYTIC LEUKEMIA. VICTOR LEVINE.

In 1913 Reschad and Schilling reported a disorder which they designated "leukemia with transitional cells," a monocytic leukemia. Dameshek, in 1930, collected thirty-three instances, nineteen of which he considered authentic.

Considerable confusion exists about monocytic leukemia. First, there has been no agreement as to the origin of the monocytes. Some consider them derivatives from myeloblasts; others, from lymphocytes, and still others, from reticulo-endothelial cells. Secondly, monocytes and their derivatives, the circulating histiocytes, are often found in large numbers in the blood stream in infectious conditions, such as kala-azar, malaria and smallpox, many cases of which are erroneously considered as monocytic leukemia. Thirdly, true myelogenous leukemia may have a transient or permanent monocytic phase. Finally, many recent reports are too incomplete or indefinite for careful analysis.

In the last two years there have been five patients with monocytic leukemia and one with myelogenous leukemia with an acute monocytic phase at Grant Hospital and Cook County Hospital. These conditions have been verified post mortem. They occurred in more than 6,000 autopsies, fifty-six of which were in cases of leukemia. Of the fifty-six cases of leukemia, thirty-five were acute. In most of the acute cases the leukemia was myelogenous, disproving the statement of Pinkus, in 1905, that all acute leukemias are lymphatic.

In acute myelogenous leukemia there is an extensive proliferation of myeloblasts in the marrow, with a predominance of myeloblasts in the blood. In acute monocytic leukemia an analogous condition might be expected, such as a marked proliferation of the reticulo-endothelial cells in the marrow and a predominance of monoblasts (the immature precursors of monocytes) in the blood. This however does not occur. Marked proliferation of the reticulo-endothelial cells usually appears as a response to infectious or metabolic disorders and does not develop into leukemia; it is a reticulo-endotheliosis. Since it differs from leukemia, the term "reticulo-endothelial leukemia" should not be applied to monocytic leukemia.

In monocytic leukemia the blood differs from that in other leukemias in that the most numerous cells are the monocytes and their descendants, the circulating histiocytes. Monoblasts must be present for a diagnosis of leukemia, but rarely are they the most numerous of the cells. The monoblast is from 15 to 40 microns in diameter and has a narrow rim of deeply basophilic cytoplasm containing a round nucleus in which the chromatin has a spongy or sheepskin-like appearance.

Oxydase stains were used in studying the cases reported here. In all but one the monocytes in the blood stream contained oxydase granules, and in the microscopic sections of this one, many of the monocytes had oxydase granules. In one patient the oxydase reaction was marked; in most instances the monocytes had fewer oxydase granules than the cells of the myelocytic series. This discrepancy is unexplained at present. With the supravital stain in two cases many of the cells were typical monocytes and histiocytes.

Of the five cases of monocytic leukemia, two were in women. Four had short clinical courses, and one was known to have been present for four months. Complaints involving the nose and throat, such as epistaxis, bleeding gums and ulcerative gums, were frequent. Several patients had petechiae; in only one was the spleen easily palpable. All the patients had moderately severe anemia. The lowest white cell count was 4,400; the highest, 120,000. The differential count in most cases disclosed the monocytes as the most numerous cells, the percentage in one instance being as high as 70. The percentage of monoblasts varied from 7 to 37. Normoblasts were frequent in some instances, and a few immature granulocytes were present in several instances. In the case of myelogenous leukemia with a monocytic phase, while the monocytes were predominant in the stains of the blood there were also a few myeloblasts and myelocytes, as well as monoblasts.

At autopsy the marrow was hyperplastic; the weight of the spleen ranged from 50 to 1,000 Gm. Differential counts of the cells in the marrow were made in all except one case in which the fixation was poor. These counts are considered the final criterion in diagnosis. In the cases of monocytic leukemia the preponderant cells were the monocytes and immature monocytoid cells. Their percentage varied from 52 to 77, whereas the highest percentage of cells of the granulopoietic series was 24. In the case of myelogenous leukemia with an acute monocytic phase, the cells of the monocytic series were 39 per cent while the granulopoietic cells were 42 per cent of the total.

ARRESTED DEVELOPMENT OF THE PRIMARY EXCRETORY DUCT. C. W. APPELBACH.

The genito-urinary tract from a full-term male infant 1 hour old was demonstrated. The two soft and boggy kidneys were enlarged symmetrically to approximately five times the normal size. The markings of the fetal lobations were irregular. The hilus of each kidney was more in the anterior surface than in the medial. The two ureters were short and the lumens narrow. The urinary bladder was only 1.5 cm. long and the trigon, particularly, was minute. The urethra had a circumference of from 2 to 3 mm., and there was an epispadias. The testes had not descended into the scrotum. There was one renal artery for each kidney with a circumference of 3 mm. When the kidneys were sectioned in the usual way, the renal pelves were narrow tubes of the same caliber as the ureters. There were two short major calices also approximately the size of the ureters. There was an abundance of renal tissue. The cortex and the columns of Bertin were more distinct than the medullary portion. The cortex was made up of multiple minute cysts. In the medulla only a few large tubes were present.

The cortex contained many small glomeruli with dilated capsules and many tubules, all separated by an edematous stroma. In sections through the medulla there were only occasional tubules.

Inasmuch as the ureter, renal pelvis and collecting tubules, part of the trigon of the urinary bladder and the vas deferens are derived from the primary excretory duct, this anomaly is explained on the basis of arrested development of that structure.

CALCIFICATION OF THE DURAL AND CEREBRAL TISSUE IN A HYDROCEPHALIC IDIOT CHILD. GEORGE RUKSTINAT.

A girl idiot, aged 3½ years, was the second child and the second idiot girl born to apparently normal parents. The first child developed poorly and died at the age of 3 years. Neither child had stigmas of mongolian idiocy. The second child died of bronchopneumonia and was markedly emaciated. Necropsy was performed about eight hours after death. The fontanels were closed, the cranial sutures were distinct, and the calvarium was symmetrical. The top half of the dura was opaque and glistening and in its dorsal third was about twice the normal thickness. The leptomeninges of the entire top of the brain were edematous; the convolutions were narrow and the sulci deep. The lateral ventricles were abnormally fluctuant from bilateral internal hydrocephalus, which had increased their maximum cross diameter to 7 cm. The larger arteries and veins of the brain were unchanged. On the right side, in the wall of the superior longitudinal sinus, 3 cm. anterior to the torcular Herophili, was a yellow-gray, firm mass 15 mm. long and from 1 to 2 mm. thick. Its long axis paralleled the sinus, and a small lateral projection lay in contact with one of the larger meningeal veins. Similar but smaller deposits occurred in the dorsal half of both cerebral hemispheres, especially at the junction of the gray and white matter. Two such masses formed ridges beneath the lining of the lateral ventricles. The masses were especially abundant in the dentate nuclei and could be traced in clusters about the main arteries in these structures. The deposits were hard and gritty with exception of the single mass in the dura.

Microscopically, the deposits contained calcium, which occurred as globules in the brain tissue and as cords along the capillaries and in the adventitia and media of the arteries. The globules formed conglomerate mulberry-like masses and, combined with short cords, formed structures like a child's jack with bulbous ends on thinner crossing and interlacing bands. In some arteries the lumen was compressed to half the diameter of a red blood cell. About the regions of densest deposit there was a marked capillary proliferation but only a slight increase in glia. Most zones about these deposits were, in fact, remarkable for their lack of reaction.

The other organs were altered only in a way compatible with the marked inanition and the bronchopneumonia. The thymus weighed only 8 Gm.

The presence of the calcified material in the outer portions of vessels and in the perivascular spaces was evidence, in some measure, of the route taken by the substance predisposing to calcification. The nature of this substance was not apparent but it seemed possible to postulate some injury to the brain at birth or as a result of the hydrocephalus which supplied the necessary base material in which calcium later accumulated. The limitation of these deposits to the brain and dura suggested a local chemical disturbance such as an altered carbon dioxide content of the tissues, although certain endocrine dysfunctions might have explained the condition.

DISCUSSION

R. H. JAFFÉ: The possibility of traumatic lesions may be considered. Lesions due to trauma of the brain at birth often cause different kinds of calcification.

G. RUKSTINAT: I have considered that. There were no reactions around the lesions.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Jan. 11, 1934

V. H. MOON, *President, in the Chair*

CYST IN A LARGE MYOMA UNDERGOING SARCOMATOUS CHANGE. LEWIS C. SCHEFFEY.

A Negress, married, aged 39, a secundipara, was admitted to the gynecologic service of the Jefferson Medical College Hospital, Jan. 9, 1933, complaining of menorrhagia, vaginal discharge, frequency of urination and abdominal enlargement. The menstrual disturbance and vaginal discharge had been present for three years; the irritability of the bladder and the abdominal enlargement were of one year's duration. Bimanual examination revealed a soft, fluctuating, freely movable and well-outlined enlargement occupying the entire pelvis and lower abdomen and extending above the umbilicus. Pregnancy and pelvic inflammatory disease having been excluded, a presumptive diagnosis of a soft myoma of the uterus or an ovarian cyst was made. The abdomen was opened on January 26, following a preliminary curettage of the uterus. The uterus was found uniformly enlarged, with a smooth, glistening surface; it had the size and appearance of a uterus seven months pregnant. The adnexae were normal. Supravaginal hysterectomy was done, the tumor being removed intact, with conservation of both adnexae.

On being incised on the anterior surface the tumor released 3,500 cc. of clear serous fluid similar to amniotic fluid. The wall of the uterus was markedly thickened, being made up of trabeculated and convoluted formations of fibrous tissue. This large cavity (12 by 8 by 8 cm.) in the uterine wall encroached on an elongated, thinned-out endometrial surface, but was encapsulated in the anterior uterine wall, being a so-called pseudocyst of the uterus; it was in a myoma that had undergone hyaline and cystic degeneration with liquefaction.

The histologic report (Dr. Crawford and Dr. Hoffman) was as follows: The uterine glands were beginning to assume serpentine formations and a few of the glands presented early secretory activity. Here and there a gland was cystically dilated and hyperplastic. The stroma was edematous and rather well vascularized. The myometrium was well vascularized and somewhat edematous. The fibrocyst was lined by a rather thick zone of cellular tissue, which was mostly made up of muscle cells intermingled with other types of cells such as spindle cells and round cells. This great cellularity gave the growth a malignant appearance. The variation in the chromatin content, size and shape of the nuclei and the mitotic figures fit into the picture of sarcoma. The clumping of cells was rather characteristic of sarcoma. This growth was more or less differentiated

in some areas from the underlying normal musculature. In some areas deep penetration by the sarcomatous growth was seen.

Postoperative roentgen examination revealed no metastatic areas in the lungs or bones. The patient was heard from recently and had remained well. This case is reported in *Surgical Clinics of North America* (**14**:143 [Feb.] 1934).

The occurrence of a large cystic myoma has been reported by R. T. Frank. He mentioned enormous tumors reported by Lihotsky, containing 3.4 liters (3,400 cc.); Lingens, weighing 45 pounds (20.4 Kg.); Webster, 87 pounds (39.4 Kg.), and Kelly and Cullen, 89 pounds (40.4 Kg.). In none of the reports of these cases was the occurrence of sarcomatous degeneration mentioned as a complicating lesion. The resemblance to pregnancy may be striking. Hartman erroneously reclosed the abdomen in such a case (reported by Frank).

CARCINOMA OF THE TAIL OF THE PANCREAS ASSOCIATED WITH POLYPOSIS AND CARCINOMA OF THE STOMACH. JOHN W. PARSONS.

A Negro, aged 39, had had syphilis of the central nervous system for five years and epigastric pain with occasional attacks of vomiting for three weeks. He was admitted to the hospital of the University of Pennsylvania in September, 1933. He was poorly nourished, with signs of tabes dorsalis and optic atrophy, and had a diffuse mass in the epigastrium. His course was steadily downward and he died three months after admission to the hospital.

Autopsy revealed a large, firm, whitish-pink mass occupying the tail of the pancreas which was poorly defined from the surrounding tissue. The lymph nodes in the region of the pancreas were greatly enlarged owing to infiltration by similar firm tissue. The liver was studded with nodules of tumor tissue, and these were confluent over a large area in the right lobe. The peritoneal surfaces of the intestine contained many small nodules, and similar tissue was observed in the suprarenal glands and kidneys.

The stomach was greatly dilated and its wall thickened. The mucosa was thickly studded with small, moderately firm, polypoid masses varying from a few millimeters to 1 cm. in diameter. There were three large ulcers on the mucosa, two of which were covered by unbroken epithelium and were apparently healing. The third was larger than the others; its center was covered by a thin layer of dirty brown necrotic material, and its edges were slightly elevated above the adjacent mucosa. The pylorus was the site of a ring of large confluent polyps which almost completely occluded its lumen.

The mass in the pancreas was composed of large, poorly differentiated, actively growing epithelial cells. There was some tendency toward glandular structure, though many areas were solid. The stroma was moderately dense with few large blood vessels. The nodules in the lymph nodes, liver, intestine, suprarenal glands and kidney conformed to this histologic structure.

The mucosa of the stomach was greatly hyperplastic, with considerable increase in the size of the epithelial cells, which contained numerous large vacuoles. The polyps were composed of such epithelium and were supported on a narrow stalk of loose fibrous tissue. Sections from the ulcerated area showed the center to be denuded of epithelium and covered by necrotic débris. The edges revealed irregular hyperplasia of the epithelium, which penetrated the basement membrane in places and extended in irregular cords into the submucosa. Under the center of the ulcer such epithelial overgrowth was especially conspicuous, and here there also was penetration of the muscularis mucosae.

There were several areas in the stomach in which cords of epithelial cells were found growing within lymphatic vessels in the subserosa. These cells resembled the cells of the tumor of the pancreas more than they did those of the carcinoma of the stomach.

The mass in the pancreas was a primary carcinoma of poorly differentiated type. The ulcerated area in the stomach showed unmistakable signs of carcinoma primary at that site. The polyps on the gastric mucosa showed no tendency toward

malignancy. The metastatic tumor nodules all resembled the pancreatic carcinoma rather than that of the stomach. It is of special note that metastases from the pancreatic tumor were found in the stomach, itself the site of a carcinoma.

ACUTE AMEBIC DYSENTERY. F. L. HARTMAN and CLARKE E. BROWN.

A white man, 41 years of age, was admitted to the Lankenau Hospital Aug. 27, 1933. He had attended a convention in Chicago from June 21 to June 26. The date of onset of the symptoms was not recalled, but during July he experienced severe attacks of abdominal pain, without nausea or loss of appetite. After the first of August he noted increasing fatigue but nevertheless continued at work until August 20. The onset then was sudden with severe pain in the abdomen and intense constant desire to defecate. The bowel movements were about twenty in twenty-four hours, containing much mucus and little blood. There was practically no rise in temperature. Tenesmus was intense. There was no vomiting. The abdominal wall was fairly rigid and sensitive to the touch. These records were supplied by Dr. R. H. Bloss, of Bethlehem.

On admission the patient was moribund. According to his wife he had always enjoyed good health except for occasional attacks of epigastric distress coming on immediately after meals for the past four or five years. These were extremely mild and were always relieved by his taking a small amount of soda. He had never had diarrhea.

The patient was semistuporous; the skin was cold, clammy and pale. The heart was moderately enlarged; there were no murmurs but the muscle tone was decidedly poor. The abdomen showed moderate distention, generalized mild tenderness and slight rigidity. Peristalsis was increased.

On rectal examination pronounced bogginess of the wall was found just inside the sphincter, and as the finger was inserted farther it met with apparent obstruction. This obstruction was due to firm ridges with apparent excavations such as one finds in an ulcerative carcinoma. However, the feel was not nodular and not hard. It gave one the impression of intussusception with the edematous bowel extending down. There was a constant discharge from the rectum of a thin, brownish-black, watery, mucoid fluid, and although the patient had marked tenesmus and bearing down there were no large stools. Examination of the fluid from the rectum showed mucus, a heavy trace of blood, absence of bile, large amounts of pus, epithelial cells and granular débris. The reaction was alkaline. Parasites were not found. The patient's death occurred the next morning.

Autopsy (by Dr. Brown) revealed generalized purulent and pseudomembranous colitis with transverse but nonperforating ulcers destroying almost the entire mucosa. The lower 6 cm. of the ileum was also involved. In sections stained with hematoxylin-eosin, iron-hematoxylin, the Giemsa stain and thionine, Endamoeba histolytica was found in abundance in all three layers of the thickened intestinal wall. Other organs were not involved.

EFFECT OF RETICULO-ENDOTHELIAL CELL BLOCKADE ON THE FORMATION OF ANTIBODIES IN RABBITS. LOUIS TUFT, with the assistance of MARY MULROONEY.

Considerable difference of opinion exists concerning the relation of the reticulo-endothelial system to the formation of antibodies as determined by blockade of the cells with inert particulate material. In the experiments reported as yielding no evidence of such a relationship the fault in the opinion of Cannon and his co-workers was either in a failure to give sufficiently large amounts of the blockading material and to continue its administration throughout the experiment to insure continued saturation of newly differentiated cells or in the use of too few animals or too large a dose of antigen. Employing these principles, they were able to show definite inhibition of the formation of hemolysin after blockading the reticulo-endothelial system with india ink.

By employing the same type of technic with slight modification we determined the effect of blockade of the reticulo-endothelial cells with india ink and trypan blue on the formation of agglutinins to the typhoid bacillus and to the paratyphoid bacilli A and B and on the formation of complement-fixing antibodies to the typhoid bacillus, the production of such antibodies in forty rabbits being stimulated by intradermal and intravenous injections of from 1 to 3 doses of mixed typhoid vaccine. Examination of the tissues of the "blocked" rabbits revealed marked infiltration of the reticulo-endothelial cells with india ink.

The results of these experiments showed fairly conclusively that this type of blockade is effective in preventing the formation of agglutinins and complement-fixing antibodies against typhoid, paratyphoid A and paratyphoid B bacilli, as shown by a suppression of both the natural and the acquired agglutinins and likewise by a failure of control animals that had previously shown ability to produce antibodies to produce them after being "blockaded." This suppression was independent of the type of blockading material employed or the route of administration of the antigen, the agglutinins being suppressed with considerable ease.

The results of these experiments supply further evidence of the importance of the reticulo-endothelial cells in relation to the formation of antibodies and emphasize the point brought out by Cannon and his co-workers that in all blockading experiments, irrespective of the material or the antigen employed, continued saturation of the reticulo-endothelial cells to suppress the activity of newly regenerated cells is essential for satisfactory results.

IMMUNIZATION OF MONKEYS AGAINST ACUTE ANTERIOR POLIOMYELITIS WITH SPECIAL REFERENCE TO ORAL IMMUNIZATION. JOHN A. KOLMER and ANNA M. RULE.

A chloroform-treated vaccine of monkey poliomyelitic spinal cord in a total dosage of 1 cc. by subcutaneous and intracutaneous injection failed to immunize two monkeys against intracerebral inoculations of the virus. Subcutaneous injections of a sodium ricinoleated vaccine appeared to produce slight immunity in one monkey while intracutaneous injections immunized two additional animals in a more convincing manner. Intracutaneous injections of an untreated vaccine successfully immunized one animal; when it was administered by a stomach tube it failed to protect two animals. A heated vaccine failed to immunize five monkeys when administered subcutaneously, intracutaneously and by stomach tube. Hexamethylamine, metaphen, mercurochrome, Pregl's solution of iodine (the solution resulting from the action of iodine on sodium carbonate solution), sodium and gold thiosulphate, sodium ricinoleate, neoarsphenamine, neutral acriflavine, tryparsamide and bismuth potassium tartrate were ineffective in the treatment of experimental poliomyelitis in monkeys. From five to eight intravenous injections of each compound were given at intervals of three days in doses per kilogram of body weight comparable in most instances to the maximum amounts given adult human beings in the treatment of various diseases.

Book Reviews

Diet and the Teeth: An Experimental Study. Part III. The Effect of Diet on Dental Structure and Disease in Man. By May Mellanby. Medical Research Council Special Report Series, No. 191. Price, 5 shillings. Pp. 180, with 46 plates. London: His Majesty's Stationery Office, 1934.

The author's former work led naturally to the study of the teeth of man. In this comprehensive report, replete with illustrations, the author points out that the procedure in man necessarily must be different from that in experiments on animals. She first describes the structure of a perfect tooth. She then reports the results of her investigations on hypoplastic teeth. It was found that a close correlation exists between external appearance and internal structure, and that there is a definite relationship between caries and hypoplastic teeth. For example, in 1,500 deciduous teeth which were subjected to a comprehensive examination, 78 per cent of those with normal dentin were free from caries, while only 6 per cent of very hypoplastic teeth were free from caries. Although the evidence for a relationship between hypoplasia and caries is weighty, the condition of many teeth could not be explained by this hypothesis. Further investigation revealed that nearly all the exceptions to the first hypothesis could be explained by assuming a change in the character of the tooth subsequent to eruption. It was thought that this change in the nature or resistance of the tooth could be accurately determined by the presence and character of the secondary dentin. Thus, the author found that only 32 of 1,500 deciduous teeth were exceptions to the two general hypotheses, namely, that primary structure and caries are directly associated, and that the reaction of teeth to caries or attrition is modified after eruption, as is indicated by the presence and character of the secondary dentin.

Next she reports dietary experiments on groups of children in order to determine whether the incidence and progress of caries are affected by diets which, in general, are rich in vitamin D, calcium and phosphorus and low in anticalcifying substances. Although the number of children in these experiments was not great, and the duration was somewhat limited, she considers the results sufficiently striking to indicate that her previous experiments on animals are reliable guides to the study of dental disease in man.

The work covers a wide field, as the author also investigated the relationship between caries and rickets and found that a group of rachitic children had an extremely high incidence of caries. As to the geographic distribution of caries, it is pointed out that there is a strong tendency for caries to develop in natives who change their way of living to that of civilization in an amazingly greater frequency than when they live in their primitive state. The importance of vitamin D, calcium and phosphorus, together with common and prolonged breast feeding, as factors tending to produce a low incidence of caries was shown in this geographic survey, as was the tendency for diets high in anticalcifying substances, as, for instance, cereals, to produce a higher incidence of caries.

This important contribution is encouraging. However, some parts of the work seem to be on somewhat firmer ground than others. It seems logical to accept the fact that a tooth would be defective if the cells were not supplied with proper materials when it was under construction, and that such a tooth would be more susceptible to caries than a normal tooth. It also seems probable that the mineral content of teeth is dependent on the mineral metabolism, and so the use of proper diets can definitely influence the incidence and spread of caries.

The portion of the work concerned with the two hypotheses is somewhat confusing, because each hypothesis tends to weaken the other. A group of teeth cannot be divided so that the condition of those of one group may be explained by one hypothesis and those of the other by a second. Both primary structure and modification of structure after eruption must be considered as factors in every

tooth, which leaves one wondering which is the more important, primary structure or subsequent diet. The statistics of the use of secondary dentin as a useful guide in determining the resistance of hypoplastic teeth are not particularly convincing. There are so many factors in the production of secondary dentin that its use as an index must always be difficult. The factors which lead to the production of the matrix are not the same as those which lead to good calcification. Indeed, in bone the reverse is found: an overgrowth of matrix is characteristic of rickets. Nevertheless, this is an important piece of work and one in which a great deal of evidence is presented of the relationship between diet, structure of the teeth and caries.

Die pathologisch-histologischen Untersuchungsmethoden. By Prof. Dr. G. Schmorl, Geh. Medizinalrat und Direktor der patholog-anatom. Abteilung am Stadtkrankenhause Dresden-Friedrichstadt. Sechzehnte neu bearbeitete Auflage. Herausgegeben von Prof. Dr. P. Geipel. Price, 30 marks. Pp. 469. Berlin: F. C. W. Vogel, 1934.

Schmorl's textbook, for many years a reliable guide for methods used in pathologic laboratories, was revised for this edition by the author before his death in 1932; Geipel made a few editorial changes subsequently. The general arrangement of the material in eighteen chapters is comparable with that in the familiar American textbook by Mallory and Wright. The methods recommended are, however, described at greater length; many are modern. The eighteen chapters describe: the examination of unfixed preparations; fixation and hardening of tissues; decalcification and defatting; the method of making injections into blood vessels; sectioning of tissues; methods of preparing frozen tissue; embedding; the ordinary stains for tissue; impregnation with metals; clearing and preservation; the special stains for particular constituents of cells and tissues; the steps required for the examination of particular pathologic changes, individual tissues, such as nerve tissues, and organs and the blood, and the demonstration and identification of bacteria, the higher species of fungi and spirochetes. A final chapter describes how animal parasites are sought and how their characteristics are ascertained. This manual has become well entrenched as a valuable guide in pathologic histology by many previous editions. This edition equals the others in merit and usefulness.

Books Received

THE CHEMISTRY OF ANTIGENS AND ANTIBODIES. J. R. Marrack, D.S.O., M.C., M.D. Medical Research Council, Special Report Series, No. 194. Paper. Price, 2s. 6d. Pp. 135, with 26 illustrations. London: His Majesty's Stationery Office, 1934.

This little monograph represents the best attempt this reviewer has seen to apply modern physicochemical principles to an analysis of the fundamental nature of immune reactions. The first chapter, on physicochemical considerations, reviews modern theories of valence and molecular structure and discusses some of the properties of proteins that are fundamental to any critical examination of immune reactions. In chapter 2, on the nature of antibodies, the author discusses such matters as the separation of antibodies, the stability of antibodies and the composition of antigen-antibody complexes. Chapter 3 deals with the specificity of antigens and includes discussions of artificial protein antigens, polysaccharides and lipids, while chapters 4 and 5 are concerned with the nature of antigen-antibody reactions. Various types of immune reactions are discussed in the light of modern concepts of valence, molecular structure and molecular orientation as applied to the study of the structure and behavior of proteins. This is an extremely interesting volume and should be of especial value in directing the attention of students of immunology to the intricate physicochemical reactions which are behind the gross changes ordinarily observed in antigen-antibody reactions. There are extensive references to the original literature for those interested in pursuing this fascinating field.

REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEAR 1932-1933. Price, 2s. 6d. Pp. 161. London: His Majesty's Stationery Office, 1934.

ADDENDA TO A BIBLIOGRAPHY OF THE HONOURABLE ROBERT BOYLE. J. F. Fulton, M.D., Sterling Professor of Physiology, Yale University. Reprinted from the Oxford Bibliographical Society Proceedings and Papers, Volume III, part 3, pp. 339-365. Paper. Gratis. Pp. 27. New Haven: Yale University School of Medicine, 1933.

STUDIES ON HISTOMONIASIS, OR "BLACKHEAD" INFECTION, IN THE CHICKEN AND TURKEY. Ernest Edward Tyzzer, Department of Comparative Pathology, George Fabyan Foundation, Medical School, Harvard University. Price, $1.25. Pp. 79, with 6 plates and 47 figures. Boston: American Academy of Arts and Sciences, 1934.

HYPOCHLORÉMIE ET ACCIDENTS POST-OPÉRATOIRES. ETUDE CLINIQUE PATHOGÉNIQUE ET THÉRAPEUTIQUE (COLLECTION MÉDECINE ET CHIRURGIE PRATIQUES, NO. 63). Mm. H. Chabanier et C. Lobo-Onell. Price, 22 francs. Pp. 146, with 9 figures. Paris: Masson et Cie, 1934.

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